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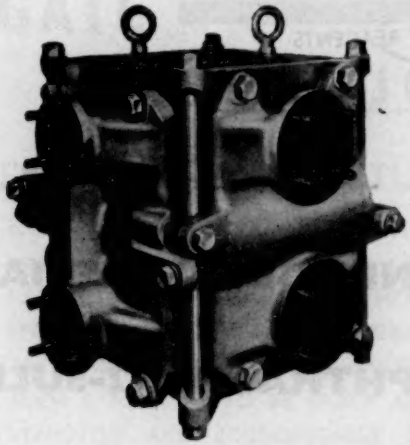

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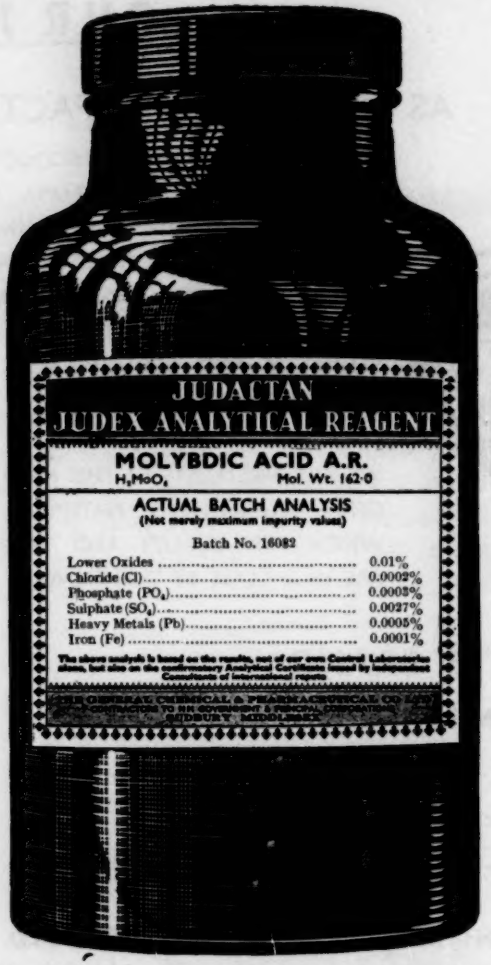

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622. *Polarisation in Conjugated Systems. Part I. The Refractions and Electric Dipole Moments of Some Derivatives of Benzene, Styrene, Diphenyl, Stilbene, and 1 : 4-Diphenylbutadiene.*

By K. B. Everard, L. Kumar, and L. E. Sutton.

The dipole moments of 44 compounds have been measured in order further to elucidate the nature of the polarisation which takes place when one or more groups are substituted into a conjugated system. Part I contains all the experimental observations. The theoretical difficulties involved in estimating distortion polarisations of compounds having large dispersions are discussed; it is suggested that the use of the so-called "calculated" $[R]_D$ values is less hazardous than that of the observed ones in such cases.

Comparison is made, when possible, between dipole moments already published and those now reported. The choice of dipole moment values from the literature is considered; and a critical list for simple benzene and paraffin derivatives is given.

It is concluded that styrene probably has a moment of *ca.* 0·1 D., and that 2 : 4 : 6-trimethylstilbene and triphenylethylene may not be quite non-polar. In the last two compounds there is evidence that conjugation is sterically inhibited.

This investigation began in 1948 when we were invited by the Chester Beatty Research Institute, Royal Cancer Hospital, London, to measure the electric dipole moments of a large number of rare compounds. Most of them were derivatives of stilbene which had been synthesised because of their physiological interest: several are either carcinogenic or inhibit the growth of tumours, according to the experimental conditions (Haddow, Harris, Kon, and Roe, *Phil. Trans.*, 1948, *A*, **241**, 147).

One purpose of the investigation was to add to the physical chemistry of these important compounds, in an attempt to bring to light any chemicophysiological relations. Related information (spectroscopic, etc.) has already been, or is about to be, published (Haddow *et al.*, *loc. cit.*; Thompson, Vago, Corfield, and Orr, *J.*, 1950, 214; Coulson and Jacobs, *J.*, 1949, 1983; Pullman, *Compt. rend.*, 1948, **226**, 486; Butler, *Nature*, 1950, **166**, 18; Beale and Liberman, to be published).

However, this aspect of the work is treated only incidentally here; the emphasis is on physicochemical problems. It was expected that the moments of some compounds would throw light on several interesting topics covered by the general title. As the investigation proceeded, it was found that certain questions were incompletely answered; so other compounds—mostly derivatives of styrene and diphenyl—were prepared.

Among the topics discussed in detail later are the dependence of the polarisation of a conjugated system, bearing a polar group, on: (i) the nature of the system (Part IV) and of the group (Part V), (ii) the position of attachment (Part III), and (iii) the presence in the molecule of other groups capable of steric interaction (Part II) or electronic interaction (Part VI).

This paper contains all the experimental details, including some optical-dispersion measurements. It was found at the outset of the work that the measured refractions of the more highly conjugated compounds were appreciably greater than those calculated by adding the refractions of the constituent fragments of the molecules. The disparity was too large to be ignored, since the resulting uncertainty in the dipole moments was in some cases about ten times the experimental error. It arises from the unusually large dispersions shown by molecules with such extensive conjugated systems; and the dispersion measurements were undertaken in order to find how the distortion polarisations could best be estimated in the peculiar circumstances.

The dipole moments which have been obtained are compared with any previously reported values; and a critical list of moments needed in the later discussion is given, with some notes on the selection of such data.

Finally, the values found for the moments of stilbene, 2 : 4 : 6-trimethylstilbene, and triphenylethylene are discussed.

Experimental.

Preparation and Purification of Materials.—Benzene. This was purified in the usual way (Everard and Sutton, *J.*, 1949, 2312).

Styrene. A B.D.H. specimen was dried ($CaCl_2$) and twice fractionated in a vacuum; the fraction of b. p. 36·5—37°/11 mm. was collected and used the same day. Beilstein's " Handbuch " (1st revision) quotes b. p. 34·2°/10 mm. and b. p. 40°/14 mm.

Benzonitrile. Fractionation of two different commercial specimens having given an unsatisfactory product, the material was made from pure benzamide (m. p. 127—128°) by heating it with phosphoric anhydride for 15 minutes and distilling the product (Buckton and Hofmann, *J.*, 1857, **9**, 255). The distillate, which melted at −14°, was redistilled over phosphoric anhydride at 192—193°, and then had m. p. −13·1° to −13·6° (Weissberger and Proskauer, " Organic Solvents," O.U.P., 1935, p. 75, give −13·1°). Before use four-fifths were slowly frozen and the rest decanted.

p-Phenylenediamine. A B.D.H. specimen was recrystallised from ether, water, and benzene–ethanol. It then melted at 141—142° (corr.). Beilstein's " Handbuch " (2nd revision) quotes 142°.

NNN'N'-Tetramethyl-p-phenylenediamine. The hydrochloride (B.D.H.) was treated with sodium hydroxide solution and warmed, and the product filtered off. The dry precipitate was thrice sublimed in a vacuum, whereafter it had m. p. 48·5—49°. Beilstein's " Handbuch " (2nd revision) quotes 50—51°.

4-Chlorostyrene. This was prepared from *p*-chloroacetophenone by reduction and then dehydration. A solution of the phenone (50 g., 0·32 mole) in ether (100 ml.) was added gradually with cooling to ethereal lithium aluminium hydride (250 ml.) (= 0·65 mole of hydrogen) (cf. Finholt, Bond, and Schlesinger, *J. Amer. Chem. Soc.*, 1947, **69**, 1199), and the mixture agitated for 15 minutes. Dilute hydrochloric acid was then cautiously added until a clear aqueous layer was obtained. The ethereal layer was separated and, together with an ethereal extract of the aqueous layer, was dried ($MgSO_4$) and evaporated. The residual oil on distillation afforded 1-*p*-chlorophenylethanol (42 g.), b. p. 87—87·5°/1 mm. (Found: C, 60·9; H, 6·1; Cl, 22·4. Calc. for C_8H_9OCl: C, 61·3; H, 5·8; Cl, 22·6%).

Potassium hydrogen sulphate (3·5 g.) and quinol (0·5 g.) were fused at 210—220° in a 25-ml. Claisen flask immersed in an oil-bath. Nitrogen, purified by passing successively through pyrogallol solution, concentrated sulphuric acid, and tubes containing potassium hydroxide pellets, was introduced below the surface of the melt, and a pressure of 90—100 mm. maintained over it. 1-*p*-Chlorophenylethanol (8 g.) was added at the rate of 1 drop/sec. The distillate, dissolved in peroxide-free ether, was washed with 5% sodium hydroxide solution and saturated calcium chloride solution, and dried ($CaCl_2$). Quinol (0·5 g.) in ether was added, the ether distilled off in a nitrogen atmosphere, clean all-glass apparatus being used, and the styrene fractionated with a 4-plate Dufton column (cf. Marvel and Schertz, *J. Amer. Chem. Soc.*, 1943, **65**, 2054; Brooks, *ibid.*, 1944, **66**, 1295). The fraction (2·5 g.) of b. p. 73·5—74·5°/6—7 mm. was used.

4-Bromostyrene. This was prepared similarly. 1-*p*-Bromophenylethanol was obtained as a colourless oil, b. p. 115—118°/1—2 mm. (Found: C, 48·1; H, 4·5; Br, 39·5. Calc. for C_8H_9OBr: C, 47·8; H, 4·5; Br, 39·8%), and 4-bromostyrene as an almost colourless oil, b. p. 94—95°/4—5 mm. (Found: C, 52·6; H, 4·1; Br, 43·5. Calc. for C_8H_7Br: C, 52·5; H, 3·8; Br, 43·7%).

The b. p.s of 4-chlorostyrene and 4-bromostyrene are markedly higher than those reported in the literature. These discrepancies were discovered only in the last stages of the preparation of the paper, and they have not yet been elucidated. It is therefore best that the dipole moments of these compounds should be regarded as provisional.

4-Nitrostyrene. This compound, prepared according to Strassburg, Gregg, and Walling (*J. Amer. Chem. Soc.*, 1947, **69**, 2141), had the same m. p., 21·4°, as they observed (Found: C, 64·5; H, 4·9; N, 9·4. Calc. for $C_8H_7O_2N$: C, 64·4; H, 4·7; N, 9·4%).

4-Dimethylaminostyrene. This was prepared similarly, except that it was recovered pure from its ethereal solution as described above for 4-chlorostyrene. It had m. p. 16·5° (Strassburg *et al.*, *loc. cit.*, give 16·8°).

β-Nitrostyrene. A B.D.H. specimen, twice recrystallised from ligroin, had m. p. 57—57·5° (Beilstein's " Handbuch " quotes 58°).

Benzidine. " AnalaR " material was twice recrystallised from ethanol and sublimed in a vacuum; it had m. p. 125° (Kofler and Lindpaintner, *Mikrochem.*, 1938, **24**, 43, give m. p. 125° *inter al.*).

NNN'N'-Tetramethylbenzidine. This was prepared by oxidising dimethylaniline (Willstätter and Kalb, *Ber.*, 1904, **37**, 3761). It was purified by being recrystallised twice from benzene and thrice from amyl alcohol, and finally sublimed in a vacuum. It had m. p. 195—196° (corr.); Beilstein's " Handbuch " quotes 193·5°, 195°, 197°, and 198°.

4-Cyanodiphenyl. This compound was made by the Sandmeyer reaction (cf. Kaiser, *Annalen*, 1890, **257**, 100) and was then recrystallised from ethanol to constant m. p., 86—86·5°; Beilstein's " Handbuch " (2nd revision) quotes 82° and 88°.

4-Bromodiphenyl. This was made and purified similarly. It had m. p. 88·5°; Beilstein's " Handbuch " (2nd revision) quotes 89—90° and 91·2°.

4-Nitrodiphenyl. A B.D.H. specimen, twice recrystallised from ethanol, melted at 113·5—114° (corr.); Beilstein's " Handbuch " (2nd revision) quotes 114—115°.

4-Dimethylaminodiphenyl. B.D.H. 4-aminodiphenyl was methylated by Bell and Kenyon's method (*J.*, 1926, 2705). The product was twice recrystallised from ethanol, and then thrice more without change of m. p., 120° (corr.); Bell and Kenyon give 123°, and Evans and Williams (*J.*, 1939, 1199) give 122°.

Stilbene. Stilbene was purified by three recrystallisations from ethanol followed by vacuum sublimation.

The remaining compounds were obtained from the Chester Beatty Research Institute. They had been prepared as described by Haddow, Harris, Kon, and Roe (*loc. cit.*), and were purified by chromatography and recrystallisation as also described there, either in Oxford or at the Institute, not more than *ca.* 1 month before examination. Light was excluded from the materials during storage and (except for red or dim white light) until dielectric-constant measurements had been completed on the solutions, owing to the danger of isomerisation; there was no evidence that this ever occurred during measurements.

The following special details may be noted. 4-Bromostilbene was found to be particularly unstable, and was recrystallised from ethanol immediately before examination. Triphenylethylene, though scrupulously purified, had a rather low m. p., but was spectroscopically pure. Spectroscopic examination also showed that the 1-*p*-dimethylaminophenyl-4-phenylbuta-1 : 3-diene used was the *trans-trans*-isomer (R. N. Beale, private communication). It is assumed from the method of preparation, and confirmed in many cases by the spectra, that all the compounds examined had *trans*-configurations (except *cis*-4-bromo-4'-nitrostilbene).

The m. p.s of the specimens used were as follows; they are uncorrected unless italicised. The numerals in Clarendon type denote the names of the compounds as given in Tables V and VI: **2**, 141—142°; **3**, 106°; **4**, 119°; **5**, 150°; **6**, 116°; **7**, 55°; **8**, 76—77°; **9**, 131—132°; **10**, 78—79°; **11**, 84—85°; **12**, 154—155°; **13**, 175—176°; **23**, *213—214°*; **29**, 138°; **30**, 81°; **31**, *200°*; **32**, *105°*; **33**, *220°*; **34**, *72°*; **35**, *98—99°*; **36**, 140°; **37**, *79°*; **38**, *255°*; **39**, *78·5—79°*; **40**, *133°*; **41**, *124°*; **42**, *51·5—52°*; **43**, 70°; **44**, *181—182°*.

Physical Measurements.—As many of the substances were available in only 0·1-g. quantities, the small-scale technique developed by Everard and Sutton (*J.*, 1951, 16) was widely employed. For the other substances the older apparatus for 1-g. quantities was used. Descriptions of, or references to, procedure will be found in the paper just cited.

In several cases, because of the insolubility of the solute, it was necessary to warm judiciously the closed vessel containing the two phases, then to cool it rapidly to *ca.* 25° and to make the dielectric-constant measurement. In this way observations could be made on somewhat supersaturated solutions.

Because they were made on dilute solutions, the accuracy of the dispersion measurements is less than could have been attained if such measurements had been the sole object of examining the compounds. Since, however, this was a subsidiary object, we were content (and often compelled) to sacrifice some accuracy so as to save time and materials. We draw conclusions only from the dispersion data as a whole, but not from any particular measurement.

Refractive-index values for solutions of compounds **1**—**13** were measured with an interferometer and later found erroneous (see Everard, Hill, and Sutton, *Trans. Faraday Soc.*, 1950, **46**, 417), but a Pulfrich refractometer with divided cell was used for the remaining compounds, except benzonitrile.

Polarisations, refractions, dispersions, and dipole moments were computed as described by Everard and Sutton (*J.*, 1951, 16), except that " calculated " values of $[R]_D$ were used for the distortion polarisations (see Discussion); these were based on data in Landolt–Börnstein's " Tabellen " (both the original work and supplementary volumes), and the following $[R]_D$ values: styrene, 36·49 (" Selected Values

TABLE I.*

Compd.	$10^4\omega$.	ε.	v.	Compd.	$10^4\omega$.	ε.	v.	Compd.	$10^4\omega$.	ε.	v.
1	4,092	2·2730	1·14483	**6**	603	2·2796	1·14527	**10**	1,212	2·2762	1·14490
	8,179	2·2737	1·14467		1,724	2·2910	1·14493		2,104	2·2788	1·14458
	14,703	2·2744	1·14450		2,454	2·2993	1·14471		5,380	2·2888	1·14407
	20,149	2·2750	1·14432		4,409	2·3204	1·14427		8,984	2·2992	1·14347
2	1,321	2·2800	1·14479	**7**	1,597	2·2742	—	**11**	960	2·2762	1·14496
	2,089	2·2841	1·14454		1,758	2·2748	1·14475		3,598	2·2845	1·14445
	7,922	2·3154	1·14313		3,108	2·2758	1·14444		4,789	2·2885	1·14424
	8,714	2·3199	1·14301		4,676	2·2773	1·14424		10,243	2·3062	1·14324
3	641	2·2738	1·14486		9,238	2·2813	1·14345	**12**	723	2·2801	—
	1,707	2·2755	1·14458	**8**	1,146	2·2750	1·14474		741	2·2802	1·14479
	2,327	2·2765	1·14446		1,727	2·2758	1·14462		1,319	2·2864	1·14463
	4,241	2·2798	1·14408		5,310	2·2822	1·14392		2,471	2·2984	1·14432
4	1,077	2·2742	1·14477		6,778	2·2848	1·14361		3,861	2·3125	1·14396
	3,716	2·2790	1·14406	**9**	1,386	2·2765	1·14497	**13**	897	2·2814	1·14470
	7,448	2·2861	1·14309		4,923	2·2863	1·14428		1,739	2·2902	1·14446
	8,815	2·2880	1·14280		6,131	2·2893	1·14406		2,181	2·2953	1·14430
5	1,927	2·2782	1·14436		9,058	2·2971	1·14353		2,944	2·3030	1·14406
	2,917	2·2808	1·14431								
	6,068	2·2898	1·14345								
	8,321	2·2963	1·14301								

* For an explanation of the method of presentation in Tables I—VI, see p. 2811.

TABLE II.

Compd.	Soln.	$10^4\omega$.	ε.	v.	$10^3\Delta n_D$.	Compd.	Soln.	$10^4\omega$.	ε.	v.	$10^3\Delta n_D$.
14	1	1,947	2·3067	1·14434	7	**29**	1	2,490	2·2768	1·14423	—
	2	2,937	2·3231	1·14413	10		2	4,673	2·2799	1·14341	—
	3	6,835	2·3915	1·14362	21		3	7,279	2·2836	1·14218	—
	4	9,806	2·4423	1·14317	32		4	8,652	—	—	99
15	1	902	2·2752	1·14632	—		5	9,119	2·2866	1·14159	—
	2	1,879	2·2781	1·14592	—	**30**	1	2,589	2·2920	1·14403	—
	3	2,440	—	1·14583	26		2	3,260	2·2969	1·14357	—
	4	3,833	2·2840	—	40		3	8,936	2·3403	1·14091	98
	5	4,262	2·2851	—	45		4	10,121	2·3492	1·14038	109
16	1	1,836	2·2745	1·14585	6	**31**	1	1,121	2·2770	1·14404	27
	2	12,533	2·2850	1·14465	81		2	5,061	2·2920	1·14218	83
	3	15,960	2·2887	1·14422	102		3	8,895	2·3065	1·14042	148
17	1	977	2·2734	1·14419	12		4	11,315	2·3156	1·13916	—
	2	3,771	2·2776	1·14320	25	**32**	1	1,500	2·2776	1·14410	29
	3	4,397	2·2791	1·14293	—		2	9,207	2·3035	1·14200	184
	4	14,254	2·2939	1·13865	69		3	11,555	2·3114	1·14131	214
18	1	3,630	2·2792	1·14392	—	**33**	1	1,560	2·2842	1·14425	29
	2	3,925	2·2803	1·14389	30		2	6,301	2·3180	1·14290	119
	3	17,201	2·3058	1·14080	104		3	7,864	2·3297	1·14236	157
	4	23,107	2·3163	1·13982	—	**34**	1	4,177	2·3117	1·14365	54
19	1	1,776	2·2794	1·14441	—	**35**	1	2,419	2·2811	1·14416	47
	2	5,371	2·2929	1·14398	53		2	10,334	2·3089	1·14284	190
	3	5,486	2·2930	1·14389	53		3	11,987	2·3143	1·14254	217
	4	6,338	2·2960	1·14383	64	**36**	1	956	2·2762	1·14516	—
20	1	1,632	2·2968	1·14597	17		2	2,071	2·2797	1·14473	—
	2	4,058	2·3330	1·14513	34		3	2,964	2·2824	1·14475	—
	3	8,026	2·3931	1·14386	79		4	4,213	2·2862	1·14439	—
21	1	1,142	2·2877	1·14431	8		5	7,932	2·2985	1·14375	—
	2	5,728	2·3483	1·14302	—		6	9,097	—	—	183
	3	6,377	2·3568	1·14284	41	**37**	1	1,812	2·2774	1·14422	28
22	1	340	2·2734	1·14644	—		2	7,245	2·2913	1·14332	109
	2	2,368	2·2777	1·14577	—		3	9,099	2·2960	1·14299	—
	3	5,660	—	—	101		4	19,835	—	—	300
	4	6,975	2·2865	1·14442	120	**38**	1	243	2·2779	1·14450	—
	5	7,146	2·2865	1·14435	131		2	877	2·2924	1·14428	32
23	1	3,543	2·2780	1·14314	—		3	1,098	2·2976	1·14419	35
	2	10,850	2·2890	1·13994	92	**39**	1	792	2·2745	1·14447	11
	3	14,866	2·2952	1·13827	134		2	6,273	2·2863	1·14347	88
24	1	2,053	2·2959	1·14413	16		3	8,311	2·2908	1·14305	117
	2	7,409	2·3585	1·14284	75	**40**	1	795	2·2835	1·14431	—
	3	11,369	2·4047	1·14182	116		2	4,764	2·3360	1·14293	93
25	1	1,424	2·2766	1·14428	18		3	5,633	2·3479	1·14269	106
	2	6,421	2·2892	1·14335	82	**41**	1	2,368	2·2736	1·14606	41
	3	10,752	2·3008	1·14254	137		2	2,923	2·2736	1·14597	48
26	1	328	2·2767	1·14621	10		3	15,629	2·2787	1·14344	238
	2	6,193	2·3406	1·14428	64		4	18,333	2·2799	1·14302	281
	3	8,429	2·3651	1·14338	96	**42**	1	1,187	2·2733	1·14438	14
27	1	3,035	2·2755	1·14598	—		2	6,815	2·2749	1·14356	71
	2	4,742	2·2773	1·14565	64		3	8,979	2·2758	1·14329	93
	3	11,083	2·2838	1·14427	165	**43**	1	4,317	2·2742	1·14423	—
	4	13,396	2·2859	1·14372	190		2	7,156	2·2756	1·14344	—
28	1	1,130	2·2790	1·14601	17		3	14,432	2·2789	1·14182	210
	2	1,375	2·2803	1·14577	22		4	20,861	2·2815	1·14038	312
	3	4,222	2·2956	1·14451	71	**44**	1	1,094	2·2767	1·14609	32
	4	6,202	2·3067	1·14354	112		2	1,265	2·2773	1·14618	35
							3	2,040	2·2799	1·14600	57
							4	3,642	2·2854	1·14573	95

of Properties of Hydrocarbons," U.S. Govt. Printing Office, 1947); diphenyl, 52·41 (von Auwers and Frühling, *Annalen*, 1921, **422**, 192); *trans*-stilbene, 65·60, and *cis*-stilbene, 61·77 (von Auwers, *Ber.*, 1935, **68**, 1346); and *trans-trans*-1 : 4-diphenylbuta-1 : 3-diene, 85 c.c. The last value has been interpolated from $[R]_\alpha$ and $[R]_\beta$ given by Smedley (*J.*, 1908, **93**, 372), and is subject to an uncertainty of *ca.* ±2 c.c. Everard, Hill, and Sutton (*loc. cit.*) inadvertently calculated $[R]_D$ values for the 4-nitro- and 4-dimethylamino-derivatives of 1 : 4-diphenylbutadiene from the refraction of the *cis-cis*-hydro-

TABLE III.

Compd.	Soln.	λ:	$10^5\Delta n_\lambda$. 6438.	5461.	5086.	4800.	4358.	$[R]_\lambda$. 6438.	5893.	5461.	5086.	4800.	4358.
20	3		79	89	95	97	123	43·6	43·7	45·1	46·0	46·7	49·6
22	3		103	108	112	114	117	64·4	64·4	65·9	66·9	67·5	68·6
25	3		130	139	148	155	180	68·3	69·4	69·9	71·2	72·3	75·7
26	3		90	93	99	104	118	58·5	59·5	59·4	60·6	61·5	64·0
27	3		154	173	182	191	221	84·1	86·1	87·2	88·9	90·2	94·7
27	4		184	200	214	221	244	83·8	84·9	86·2	88·0	89·3	92·4
28	4		109	115	127	134	144	81·2	82·1	83·1	86·6	88·5	91·7
29	4		90	104	104	112	118	71·0	72·8	74·0	74·4	76·1	78·0
30	4		101	118	121	126	148	76·4	78·2	80·1	80·9	82·2	86·6
31	3		142	160	170	193	—	86·8	88·2	90·6	93·2	98·0	—
32	3		200	241	258	284	354	92·4	92·7	96·4	99·0	102·6	112·1
33	3		147	171	188	211	269	91·7	94·0	97·0	100·4	105·1	116·6
35	3		209	233	262	288	383	96·2	97·6	99·9	103·8	107·4	119·3
36	5		175	199	211	230	292	86·5	87·8	90·5	92·5	95·5	104·8
37	4		285	314	340	—	458	91·9	93·4	94·8	97·1	—	106·9
39	3		105	121	131	140	164	93·6	96·3	97·4	99·7	101·9	107·1
41	4		267	290	295	311	—	64·9	66·0	66·7	67·3	68·6	—
42	3		90	91	98	95	103	77·9	78·8	78·9	80·4	80·3	82·4
43	4		307	322	331	338	381	89·9	90·6	91·7	92·9	93·8	97·6
44	3		—	—	—	—	117	—	111·9	—	—	—	155·4
44	4		85	101	119	132	—	104·9	109·3	112·2	117·4	124·9	—

TABLE IV.

Compd.	$[R]_D$, obs.	$[R]_D$, calc.	$E[R]_D$.	D ←	± →	$[R]_\infty$.	$[R]_D$, calc., $-[R]_\infty$.
14	32·2	—	—	—	—	—	—
15	33·2	35·0	−1·8	—	—	—	—
16	55·7	55·5	0·2	—	—	—	—
17	43·9	44·3	−0·4	—	—	—	—
18	42·5	41·7	0·8	—	—	—	—
19	52·3	51·2	1·1	—	—	—	—
20	43·6	43·1	0·5	4·8	1	38·8	4·3
21	43·1	43·1	0	—	—	—	—
22	64·6	61·3	3·3	4·7	1	59·9	1·4
23	60·5	60·2	0·3	—	—	—	—
24	57·6	57·8	−0·2	—	—	—	—
25	69·4	67·1	2·3	5·8	1	63·6	3·5
26	58·8	59·0	−0·2	5·0	1·5	53·8	5·2
27	85·3	81·7	3·6	7·5	0·3	77·8	3·5
28	82·1	77·8	4·3	9·5	1·5	72·6	5·2
29	72·8	73·4	−0·6	6·4	1	66·4	7·0
30	78·0	76·2	1·8	7·6	1	70·4	5·8
31	87·4	80·0	7·4	10·6	2	76·8	3·2
32	93·3	85·5	7·8	12·3	2	81·0	4·5
33	93·6	85·5	8·1	14·2	1·5	79·3	6·2
34	~69·4	71·0	−1·6	—	—	—	—
35	97·6	89·7	7·9	13·2	2	84·4	5·3
36	87·8	80·3	7·5	9·6	1·5	78·2	2·1
37	93·4	90·1	3·3	8·2	1	85·1	5·0
38	~114	86·9	27	—	—	—	—
39	96·3	94·7	1·6	10·8	0·5	85·5	9·2
40	~88·2	79·1	9·1	—	—	—	—
41	65·8	(59·2)	(6·6)	4·4	0·5	61·4	(−2·2)
42	78·7	80·0	−1·3	3·7	1	75·0	5·0
43	90·6	90·7	−0·1	5·6	0·5	85·0	5·7
44	109·1	99·7	9·4	14·3	4	94·8	4·9

carbon, instead of the *trans-trans* one. The distortion polarisation used for 4-dimethylamino-2′ : 4′ : 6′-trimethylstilbene was based on $[R]_D$ for 2 : 4 : 6-trimethylstilbene.

The uncertainties in the dipole-moment values caused by errors in experimental observation only are estimated not to exceed ±0·02 D., save for 2-dimethylaminostilbene (±0·05 D.), 3-cyanostilbene, of which only enough to make up one solution was available (~ ±0·05 D.), and the hydrocarbons, which are considered separately.

All dipole moments are in Debye units, and all refractions, etc., in c.c.

Results.—These are presented as before (*J.*, 1951, 16). To save space and facilitate cross-referencing, each compound has been allotted an identity number, printed in Clarendon type; the key to the numbering will be found in Tables V and VI. Also, each solution of compounds 15—44 has been numbered

(key : Table II) to save repeating concentrations in Table III. Derivatives of each hydrocarbon are arranged alphabetically, those of benzene appearing first, then of styrene, then of diphenyl, then of stilbene, and finally of diphenylbutadiene.

TABLE V.

		ε_1'.	a.	v_1'.	$-10^3\beta$.	${}_\pi P$.	$[R]_D$, calc.	μ.
1	Styrene	2·2726	0·126	1·14494	31	37·0	36·5	<0·3
2	4-Acetylstilbene	2·2728	5·396	1·14508	242	285·5	75·8	3·20
3	2-Aminostilbene	2·2727	1·663	1·14497	212	115·4	70·1	1·49
4	3-Aminostilbene	2·2725	1·782	1·14507	263	116·8	70·1	1·51
5	4-Aminostilbene	2·2727	2·833	1·14486	224	157·7	70·1	2·07
6	4-Cyanostilbene	2·2727	10·788	1·14539	261	470·7	71·0	4·42
7	2-Dimethylaminostilbene	2·2729	0·921	1·14502	171	103·5	80·3	1·07
8	3-Dimethylaminostilbene	2·2728	1·773	1·14497	200	137·3	80·3	1·67
9	4-Dimethylamino-2′ : 5′-dimethylstilbene	2·2728	2·697	1·14522	189	199·2	90·1	2·31
10	4-Dimethylamino-2′-ethylstilbene	2·2726	2·964	1·14504	177	212·7	90·1	2·45
11	4-Dimethylamino-2′-methylstilbene	2·2728	3·261	1·14512	184	213·6	85·2	2·51
12	4-Nitrostilbene	2·2727	10·342	1·14498	264	497·5	72·2	4·56
13	1-*p*-Nitrophenyl-4-phenylbuta-1 : 3-diene	2·2724	10·365	1·14498	309	552·6	91·6	4·75

TABLE VI.

		ε_1'.	a.	v_1.	v_1'.	$-10^3\beta$.	$10^3\gamma$.	${}_\pi P$.	μ.
14	Benzonitrile	2·2728	17·316	1·14462	1·14461	147	32	366·7	4·05
15	*p*-Phenylenediamine	2·2726	2·939	1·14650	1·14653	300	104	87·1	1·60
16	*NNN′N′*-Tetramethyl-*p*-phenylenediamine	2·2727	0·997	1·14609	1·14608	116	66	81·2	1·12
17	4-Bromostyrene	2·2727	1·515	1·14465	1·14465	420	48	91·7	1·52
18	4-Chlorostyrene	2·2728	1·902	1·14471	1·14470	217	60	87·9	1·50
19	4-Dimethylaminostyrene	2·2728	3·698	1·14462	1·14460	126	99	147·0	2·17
20	β-Nitrostyrene	2·2724	15·009	1·14655	1·14652	335	97	457·2	4·50
21	4-Nitrostyrene	2·2727	13·196	1·14465	1·14644	283	64	408·6	4·23
22	Benzidine	2·2728	1·943	1·14650	1·14652	302	178	113·6	1·60
23	4-Bromodiphenyl	2·2726	1·512	1·14467	1·14467	432	88	115·9	1·65
24	4-Cyanodiphenyl	2·2725	11·630	1·14470	1·14468	251	104	440·0	4·33
25	4-Dimethylaminodiphenyl	2·2727	2·599	1·14465	1·14461	193	127	152·4	2·04
26	4-Nitrodiphenyl	2·2729	10·936	1·14636	1·14635	347	107	457·3	4·41
27	*NNN′N′*-Tetramethylbenzidine	2·2726	0·998	1·14661	1·14664	215	144	111·7	1·21
28	4-Amino-4′-bromostilbene	2·2728	5·458	1·14650	1·14649	475	180	336·3	3·56
29	4-Bromostilbene	2·2728	1·503	1·14526	1·14526	408	114	130·2	1·67
30	*cis*-4-Bromo-4′-nitrostilbene	2·2724	7·579	—	1·14520	479	108	494·2	4·52
31	*trans*-4-Bromo-4′-nitrostilbene	2·2728	3·792	1·14465	1·14462	479	161	277·3	3·11
32	2-Chloro-4′-dimethylaminostilbene	2·2726	3·353	1·14459	1·14456	280	190	229·0	2·65
33	4-Chloro-4′-dimethylaminostilbene	2·2728	7·216	1·14465	1·14468	290	197	415·6	4·02
34	3-Cyanostilbene	—	9·34	1·14467	—	244	130	416	4·12
35	4-Diethylaminostilbene	2·2728	3·483	1·14465	1·14462	174	181	237·5	2·69
36	4-Dimethylaminostilbene	2·2729	3·220	1·14526	1·14526	193	201	198·6	2·41
37	4-Dimethylamino-2 : 2′-dimethylstilbene	2·2728	2·561	1·14459	1·14457	173	159	193·9	2·25
38	4-Dimethylamino-4′-nitrostilbene	2·2726	22·731	1·14459	1·14459	360	342	1210·4	7·42
39	4-Dimethylamino-2′ : 4′ : 6′-trimethylstilbene	2·2728	2·170	1·14455	1·14459	182	141	184·5	2·11
40	4-Methoxy-4′-nitrostilbene	2·2728	13·309	1·14459	1·14458	341	192	700·5	5·51
41	Stilbene	2·2726	0·394	1·14655	1·14654	194	151	64·4	(0)
42	2 : 4 : 6-Trimethylstilbene	2·2728	0·327	1·14450	1·14452	138	105	80·4	<0·4
43	Triphenylethylene	2·2726	0·431	—	1·14516	230	149	90·6	<0·3
44	1-*p*-Dimethylaminophenyl-4-phenylbuta-1 : 3-diene	2·2728	3·468	1·14630	1·14631	158	260	236·0	2·58

DISCUSSION.

Table IV gives some values of the exaltations of molar refractions for Na_D light, expressed as $E[R]_D = [R]_D$, obs., $-[R]_D$, calc. The calculated values have been obtained, not from atomic refractions as is sometimes done, but from the refraction of the parent hydrocarbon plus a value for each of the substituents; and the latter is taken as the difference between the refractions of the benzene derivative and of benzene itself.

Because atom polarisations (${}_AP$) cannot often be measured, it is often assumed that the error in neglecting them is just balanced by the error arising from failure to extrapolate molar refractions to infinite wave-length in order to obtain the true electron polarisation, ${}_\pi P$. The second error is equal to the molar dispersion, $\mathbf{D} = [R]_D - [R]_\infty$, as it was defined by Bauer

and Fajans (*J. Amer. Chem. Soc.*, 1942, **64**, 3023). Some of the exaltations in Table IV are sufficiently large as to suggest that the approximation, ${}_{A}P = \mathbf{D}$, is invalid.

Just as the approximation is unreliable when ${}_{A}P$ is abnormally large (Coop and Sutton, *J.*, 1938, 1269), so with **D**. It has been suggested (Everard, Hill, and Sutton, *Trans. Faraday Soc.*, 1950, **46**, 417) that the best compromise in these circumstances is to take as the distortion polarisation (${}_{E}P + {}_{A}P$) the *calculated* value of $[R]_{D}$ (as defined above). If this is done, the allowance implicitly made for ${}_{A}P$ is $[R]_{D}$ (calc.) $-[R]_{\infty}$. When this quantity is calculated for the 18 compounds in this series for which the necessary data exist, it is found in 15 cases to be 5 ± 2 c.c. (Table IV). This seems a more reasonable estimate of the atom polarisation of such compounds as these than the larger and more variable one of 4—14 c.c. provided by the quantity **D**.

It is important to note that, if calculated $[R]_{D}$ values are used for distortion polarisations, they should not be based on atomic refractions except for very simple compounds. For example, Angyal and Le Fèvre have given the calculated molar refraction of anthranyl methyl ether (9-methoxyanthracene) as 61·5 c.c. (*J.*, 1950, 562), which is lower than both the observed refraction and the total polarisation of anthracene itself [67 and 67·9 c.c., respectively (Campbell, Le Fèvre, Le Fèvre, and Turner, *J.*, 1938, 404). Steiger, however, gives the former as 65·4 c.c. (see *Ber.*, 1923, **56**, 998, and references therein)]. It should be *ca.* 6 c.c. higher {cf. $[R]_{D}$ (obs.) for 9 : 10-dimethoxyanthracene, 79·8 c.c.; Everard and Sutton, *J.*, 1951, 16}. The discrepancy arises from the use of atomic refractions, and leads to a dipole moment value 0·2 too high.

Comparison with Previous Work.—In Table VII are given the dipole moments of compounds which have been examined before, under μ (ii), together with the values obtained in the present work, under μ (i), for comparison.

TABLE VII.

Compound.	μ. (i.)	μ. (ii.) *	References and remarks.†
Styrene	<0·3	0—0·37	" Tables "; von Hippel and Wesson, *Ind. Eng. Chem.*, 1946, **38**, 1121.
4-Bromostyrene	1·52	1·35	Otto and Wenzke, *J. Amer. Chem. Soc.*, 1935, **57**, 294.
4-Chlorostyrene	1·50	1·28	*Idem, ibid.*
β-Nitrostyrene	4·50	4·27,‡ 4·48	Goebel and Wenzke, *ibid.*, 1938, **60**, 697; Bergmann, *J.*, 1936, 402.
Benzonitrile	4·05	3·74—4·02	11 Values in benzene, all ⩾15 years old : " Tables."
p-Phenylenediamine	1·60	0—1·56	Very discordant values : " Tables."
Tetramethyl-*p*-phenylene-diamine	1·12	1·23	Weissberger and Sängewald, *Z. physikal. Chem.*, 1929, *B*, **5**, 237.
Tetramethylbenzidine	1·21	1·25	*Idem, ibid.*
Benzidine	1·60	1·3—1·43	" Tables "; Sahney, Beri, Sarna, and Singh, *J. Ind. Chem. Soc.*, 1949, **26**, 329.
4-Bromodiphenyl	1·65	1·64	Le Fèvre and Le Fèvre, *J.*, 1936, 1130.
4-Nitrodiphenyl	4·41	4·17, 4·28	*Idem, ibid.*; Næshagen, *Z. physikal. Chem.*, 1934, *B*, **25**, 157. The cause of the discrepancy is obscure.
Stilbene	(0)	0	Eide and Hassel, *Tids. Kjemi Berg.*, 1930, **10**, 93; Smyth and Dornte, *J. Amer. Chem. Soc.*, 1931, **53**, 1296.
Triphenylethylene	<0·3	0·6	*Idem, ibid.*
4-Dimethylamino-4′-nitro-stilbene	7·42	8·3 §	Weizmann, *Trans. Faraday Soc.*, 1940, **36**, 978. This value is based on one very dilute solution only.
4-Methoxy-4′-nitrostilbene	5·51	7·8	*Idem, ibid.* An ε–ω plot of the earlier work is much more erratic than that now obtained.

* These measurements were carried out in benzene solution unless otherwise stated.

† The reference " Tables " alludes to Wesson's " Tables of Electric Dipole Moments," Technology Press, 1948.

‡ Measured in dioxan. § Measured in 1-methylnaphthalene.

The Choice of Dipole Moment Values from the Literature.—In this series of papers it has been necessary to select a considerable number of dipole moment values from the literature. Examination of any tables of dipole moments (*e.g.*, Wesson, *op. cit.*, Technology Press, 1948) reveals a most troublesome degree of disagreement between the measurements of different investigators; and until recently, few attempts have been made to elucidate the causes of disagreement. Some of the discrepancies are, of course, due to solvent effects, but they often occur even between measurements with the same solvent at the same temperature. The chief causes (apart from the use of impure materials and unsuitable technique or apparatus) are the computation of

polarisations at infinite dilution by unreliable methods [the importance of this has recently been stressed by Everard, Hill, and Sutton (*Trans. Faraday Soc.*, 1950, **46**, 417), *inter al.*], the different allowances made by different investigators for atom polarisation, and the use of values of the universal constants N and k which have since been revised.*

Discrepancies due to these three causes, which are to be especially suspected in early work, can always be corrected *a posteriori*, provided that experimental details are published. Recalculation is arduous, however, and has been attempted only on a very limited scale (*e.g.*, by Halverstadt and Kumler, *J. Amer. Chem. Soc.*, 1942, **64**, 2988, and by Smith and Cleverdon, *Trans. Faraday Soc.*, 1949, **45**, 109). Consequently, no *critical* tables of dipole moments exist, and users of ordinary tables are obliged to exercise personal judgment or else to re-examine compounds themselves.

We give the following general rules as a guide, though fortunately they do not always apply: (i) Certain moments in solution have been given to as many as four decimal places; the third and the fourth should be ignored. (ii) Moments >1 required accurate to $<\pm 0{\cdot}1$ should be recalculated (if previously obtained from the extrapolation of polarisation–concentration graphs); those <1 required accurate to $<\pm 0{\cdot}1$, and those >1 required accurate to $<\pm 0{\cdot}05$

TABLE VIII.

Dipole moments in benzene solution at 25°.

Group:	NO_2.	Ac.	CN.	NH_2.	NMe_2.	Br.	Cl.	F.	I.	Me.
Alkyl derivative	3·25	2·75	3·60	1·32	0·86	2·00	2·01	1·89	1·92	0
Range of uncertainty...	3·1—3·3	±0·05	3·5—3·65	?	?	±0·1	±0·1	?	±0·1	—
No. of vals. published [a]	4	25	7	9	1	22	14	2	16	—
Phenyl derivative	4·01 [b]	2·96 [c]	4·05 [d]	1·52 [e]	1·61 [f]	1·57 [g]	1·60 [h]	1·48 [i]	1·42 [j]	0·35 [k]
Range of uncertainty...	3·98—4·02	±0·02	±0·01	±0·01	±0·01	±0·02	±0·01	±0·01	±0·01	±0·05

[a] Sources: Wesson, *op. cit.*; Few and Smith, *J.*, 1949, 2663; Barclay, Le Fèvre, and Smythe, *Trans. Faraday Soc.*, 1951, **47**, 357. [b] Nitrobenzene has been the subject of a detailed investigation by Smith and Cleverdon (*Trans. Faraday Soc.*, 1949, **45**, 109), who, however, make a large allowance for atom polarisation. We take their value for ${}_TP$, but put ${}_DP = [R]_D$. Le Fèvre (*ibid.*, 1950, **46**, 1) has measured no fewer than 111 solutions, divided into three sets, but fails to get internal consistency (${}_TP$ values of 354·8, 356·1, and 358·6 c.c.). [c] Bentley, Everard, Marsden, and Sutton, *J.*, 1949, 2957. Le Fèvre and Le Fèvre give 2·89 (*J.*, 1950, 1829), but this value is clearly a mistake for 2·97 (confirmed by personal communication). [d] Present work. [e] Le Fèvre, Roberts, and Smythe have measured 13 solutions, giving $\mu = 1{\cdot}51_5$ (*J.*, 1949, 902), and Few and Smith, 16 solutions, giving $\mu = 1{\cdot}52_7$ (*ibid.*, p. 753); recalculated. [f] Few and Smith (*ibid.*); Marsden and Sutton (*J.*, 1936, 599); recalculated. Barclay, Le Fèvre, and Smythe (*loc. cit.*). [g] Otto and Wenzke (*Ind. Eng. Chem. Anal.*, 1934, **6**, 187) and Le Fèvre and Le Fèvre (*J.*, 1936, 1130); recalculated. Brown and De Vries (*J. Amer. Chem. Soc.*, 1951, **73**, 1811). [h] Le Fèvre (*loc. cit.*) (45 solutions); Curran (*J. Amer. Chem. Soc.*, 1942, **64**, 830) and Spinrad (*ibid.*, 1946, **68**, 617); recalculated. Brown and De Vries (*loc. cit.*). [i] Leonard and Sutton (*ibid.*, 1948, **70**, 1564) give 1·46 (1·48, recalculated), the value 1·53 given in this paper being a misprint for 1·43; Freiser, Hobbs, and Gross (*ibid.*, 1949, **71**, 111) give 1·47. Le Fèvre and Le Fèvre give 1·48 (recalculated), and Brown and De Vries, 1·50 (*locc. cit.*). [j] Saxby, personal communication. This value differs markedly from previous ones. [k] This value, being small, is difficult to fix with certainty. Le Fèvre, Le Fèvre, and Robertson give 0·34, but no details (*J.*, 1935, 480). Dielectric-loss measurements give 0·30—0·32 (Whiffen and Thompson, and Cripwell and Sutherland, *Faraday Soc. Discussion* on "Dielectrics," 1946, pp. 114, 122, 149). Vapour-phase measurements (probably comparable in this case) give 0·35 (McAlpine and Smyth, *J. Amer. Chem. Soc.*, 1933, **55**, 453) and 0·37 (Baker and Groves, *J.*, 1939, 1144).

should be remeasured with suitable precautions. (iii) Moments $<0{\cdot}4$ are indistinguishable from zero.

Further information about the reliability of a measurement can be obtained by plotting a dielectric constant–concentration graph, and seeing whether it extrapolates to the ϵ_1 value which the authors give; if not, unless Halverstadt and Kumler's method of computation (*loc. cit.*) had been used, the moment quoted is likely to be unreliable. Also, except for highly polar compounds, a marked (apparent) dependence of polarisation on concentration is usually indicative of error.

All dipole-moment values taken from the literature and cited in this series of papers have been recalculated, where possible and useful, from the experimental observations on which

* We take $N = 6{\cdot}0226 \times 10^{23}$ mole^{-1} and $k = 1{\cdot}3806$ erg deg.$^{-1}$ (Kaye and Laby, "Physical and Chemical Constants," Longmans, Green & Co., 10th edn., 1948), giving $\mu = 0{\cdot}2212\sqrt{{}_0P}$ at 25°; the latest revision (Bearden and Watts, *Physical Rev.*, 1951, **81**, 73) does not alter this.

they were based, the same assumptions being used about N, k, and ${}_DP$ as have been made in treating the measurements reported in this paper for the first time.

It is convenient to collect together some of these values which are used in Parts II—VI, *viz.*, those which refer to monosubstituted derivatives of paraffin hydrocarbons and of benzene (Table VIII). The former set does not refer to the derivatives of any particular paraffin, because it is needed in the estimation of mesomeric moments; so greater weight has been attached, when practicable, to observations on compounds with large groups, which might be expected to have much the same electrostatic polarisability as a benzene ring.

Dipole Moments of Stilbene, 2 : 4 : 6-Trimethylstilbene, Triphenylethylene, and Styrene—The total polarisation of stilbene is $64{\cdot}4 \pm 0{\cdot}5$; $[R]_D$ exceeds this by 1·4; and $[R]_\infty$ is $61{\cdot}4 \pm 0{\cdot}5$. It is clear that **D** exceeds ${}_AP$. The atom polarisation of a molecule such as this may be estimated additively (Coop and Sutton, *J.*, 1938, 1269; Audsley and Goss, *J.*, 1941, 864). That of ethylene is 0·4 (Watson and Ramaswamy, *Proc. Roy. Soc.*, 1936, *A*, **156**, 144), and that of benzene is 1·5 [from ${}_TP$ and $[R]_\infty$ of liquid. However, Groves and Sugden give 1·1 (*J.*, 1934, 1094), and Cartwright and Errera, 0·55 (*Acta Physicochim. U.R.S.S.*, 1935, **3**, 649)]. Hence, that of stilbene should be *ca.* 3·4. As ${}_TP - [R]_\infty$ is 3·0, ${}_OP$ is evidently very near to zero. Such non-polarity is, of course, in accordance with the symmetrical nature of the molecule as shown by *X*-ray examination (Robertson and Woodward, *Proc. Roy. Soc.*, 1937, *A*, **162**, 568).

In contrast, the total polarisations of 2 : 4 : 6-trimethylstilbene ($80{\cdot}4 \pm 1$) and of triphenyl ethylene ($90{\cdot}6 \pm 0{\cdot}8$) are not less than their $[R]_D$ (obs.) values (78·7 and 90·6, respectively): their $[R]_\infty$ values are $75{\cdot}0 \pm 1$ and $85{\cdot}0 \pm 1$, so the values of ${}_TP - [R]_\infty$ are 5·4 and 5·6. Calculated atom polarisations are 3·7 and 4·9 (each methyl group is regarded as contributing 0·1: Audsley and Goss, *loc. cit.*). It is therefore possible that these two unsymmetrical molecules may be slightly polar (moments of $>0{\cdot}4$ and $>0{\cdot}3$, respectively).

The exaltation of 2 : 4 : 6-trimethylstilbene is 1·3 less than that of stilbene, which indicates that there is less conjugation. That of triphenylethylene is about the same, suggesting that the introduction of an extra phenyl group does not here increase the conjugation. These two facts can be readily ascribed to steric influences which would cause the systems to be non-coplanar (cf. Part II).

The total polarisation of styrene is $37{\cdot}0 \pm 0{\cdot}3$. Extrapolation of the molar refractions given in Landolt–Börnstein's "Tabellen" yields the value 34·5 for $[R]_\infty$. The calculated atom polarisation is 1·9; whence the moment is 0·17, though unavoidable uncertainties make any value up to 0·3 possible. Von Hippel and Wesson obtain the value of $0{\cdot}12 \pm 0{\cdot}03$ by the dielectric-loss method (*Ind. Eng. Chem.*, 1946, **38**, 1121); this value is probably more reliable than any obtainable in the orthodox manner (see, however, Heston and Smyth, *J. Amer. Chem. Soc.*, 1950, **72**, 99, and Whiffen, *Trans. Faraday Soc.*, 1950, **46**, 124, for a possible complication). Torkington has concluded from the infra-red spectrum of styrene that "there is a resultant negative charge on the terminal carbon atom of the vinyl group . . . which will be associated with *meta*-substitution in the phenyl nucleus" (*Nature*, 1949, **163**, 179). An indirect argument that styrene has a moment of *ca.* 0·12 (vinyl group negative) is given in Part IV. The balance of evidence, then, is that styrene is a slightly polar molecule.

This result is of considerable theoretical interest, because, according to simple molecular-orbital theory, alternant hydrocarbons (such as the above) should be non-polar (Coulson and Rushbrooke, *Proc. Camb. Phil. Soc.*, 1940, **36**, 193). However, Laforgue (*J. Chim. physique*, 1951, **48**, 17) has very recently refined the earlier calculations by applying ten different kinds of correction, and has obtained a moment of 0·15 for styrene, the vinyl group being negative. The agreement with the experimental value is very satisfactory, though it should be remembered that the range of uncertainty in each is large.

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623. *Polarisation in Conjugated Systems. Part II. Steric Hindrance in Derivatives of 4-Dimethylaminostilbene.*

By K. B. Everard and L. E. Sutton.

The exaltations and dipole moments of the following derivatives of 4-dimethylaminostilbene are discussed: 2′-chloro-, 2′-methyl-, 2′ : 5′-dimethyl-, 2 : 2′-dimethyl-, 2′-ethyl-, and 2′ : 4′ : 6′-trimethyl-. The conjugation is found to decrease in this order. This is attributed to steric hindrance.

Hampson and his co-workers (*J.*, 1937, 10; 1939, 981) were the first to show that the anomalous dipole moments of mesitylene and durene derivatives were due to the steric inhibition of resonance in the molecules, and their work has been extended by Kadesch and Weller (*J. Amer. Chem. Soc.*, 1941, **63**, 1310) and by Bentley, Everard, Marsden, and Sutton (*J.*, 1949, 2957).

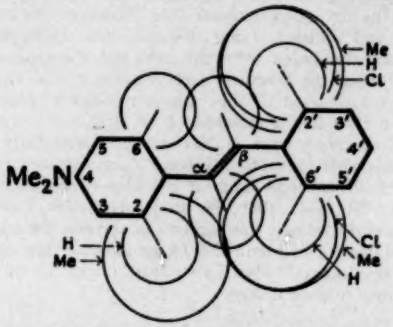
The moments of some alkyl derivatives of 4-dimethylaminostilbene have now been measured, together with their molar refractions (Part I); and both show anomalies attributable to steric inhibition of resonance. The results are collected in the table.

Exaltations and dipole moments of 4-dimethylaminostilbene derivatives.

	$E[R]_D$*	μ (obs.).	μ (expected).
4-Dimethylaminostilbene	7·5	2·41	—
2′-Chloro-4-dimethylaminostilbene	7·8	—	—
4-Dimethylamino-2′-methylstilbene	—	2·51	2·60
4-Dimethylamino-2′ : 5′-dimethylstilbene	—	2·31	2·41
4-Dimethylamino-2 : 2′-dimethylstilbene	3·3	2·25	> 2·41
4-Dimethylamino-2′-ethylstilbene	—	2·45	2·73
4-Dimethylamino-2′ : 4′ : 6′-trimethylstilbene	1·6	2·11	2·41

* Exaltations are expressed relative to that of stilbene, taken as 0 c.c. (see Part I, Discussion, p. 2812).

The molar exaltations of 4-dimethylaminostilbene and of both its 2′- and its 4′-chloro-derivatives are much the same (the last is 8·1), whereas those of the 2 : 2′-dimethyl and 2′ : 4′ : 6′-trimethyl derivatives are markedly less. These figures indicate (i) that there is negligible inhibition of conjugation in the chloro-compounds, but appreciable inhibition in the



Dimensions are taken from Pauling, "Nature of the Chemical Bond," Cornell, 1945, *and from Robertson and Woodward,* Proc. Roy. Soc., 1937, *A*, **162**, 568.

methyl compounds, and (ii) that two *o*-methyl groups on the same ring are more effective than one on each ring. This is in accordance with expectation. Pauling gives the van der Waals radius of a chlorine atom as 1·8 A., and that of a methyl group as 2·0 A.; and examination of scale models demonstrates the greater effectiveness of the former combination of two methyl groups than of the latter (see figure).

The dipole moments give the same indications. The "expected" values are calculated vectorially without allowing for inhibition of resonance; it is assumed that a methyl group

substitution moment is the same as that of toluene (0·35), and that an ethyl group moment is the same as that of ethylbenzene (0·58; Baker and Groves, *J.*, 1939, 1144). The direction of the moment of the parent compound, 4-dimethylaminostilbene, is considered in Part IV; and that of the 2'-chloro-derivative in Part VI.

It is seen that the steric effect of the several substitutions appears to increase in the order of arrangement in Table I. Conclusions drawn by Haddow, Harris, Kon, and Roe (*Phil. Trans.*, 1948, *A*, **241**, 147) from a study of the ultra-violet absorption spectra of some of the substances are similar to ours, except that the effect of a single *o*-methyl group could not be positively established. The present results support the hypothesis put forward in that paper, that such compounds show growth-inhibitory activity only when the stilbene system is coplanar.

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624. *Polarisation in Conjugated Systems. Part III. The Dipole Moments of Positional Isomers of Some Stilbene and Diphenyl Derivatives.*

By K. B. EVERARD and L. E. SUTTON.

The effect on the dipole moment of the position of substitution of a polar group in stilbene or diphenyl is examined. *para*-Substitution by the Cl, NO_2, NH_2, NMe_2, and CN groups gives a moment larger than that of the corresponding derivative of benzene; *meta*-substitution gives a moment about the same; and *ortho*-substitution gives one which is lower. This is explained in terms of resonance. The moment of 2-dimethylaminostilbene is exceptionally small, because the dimethylamino-group is sterically prevented from conjugating with the aromatic system.

SUFFICIENT dipole moments are now known of positional isomers of derivatives of the two hydrocarbons, stilbene and diphenyl, to allow a general statement to be made about the effect on polarity of the position of substitution. The available data are given in the table, and the

	Position of substitution: 4.	3.	2.	Ph.[a]
Chlorodiphenyl	1·64 [b,c]	1·64 [b]	1·45 [b,d]	1·60
Nitrodiphenyl	4·41 [e]	3·90 [f]	3·81 [g]	4·01
Aminodiphenyl	1·83 [h]	—	1·42 [i]	1·52
Aminostilbene	2·07 [e]	1·51 [e]	1·49 [e]	1·52
Dimethylaminostilbene	2·41 [e]	1·67 [e]	1·07 [e]	1·61
Cyanodiphenyl	4·33 [e]	—	3·81 [j]	4·05
Cyanostilbene	4·42 [e]	4·12 [e]	—	4·05

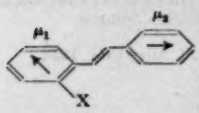
[a] All values in this column are taken from Table VIII, Part I. [b] Weissberger's second value (Hampson and Weissberger, *loc. cit.*) is assumed to supersede his first one (Weissberger and Sängewald, *Z. physikal. Chem.*, 1933, *B*, **20**, 145). [c] Literature values are: 1·5$_3$ (*idem*, *ibid.*), 1·63 (Næshagen, *ibid.*, 1934, *B*, **25**, 157), 1·63 (Hampson and Weissberger, *loc. cit.*), and 1·56 (Le Fèvre and Le Fèvre, *J.*, 1936, 1130). The last authors omit details of purity: ω–ϵ plots of their measurements differ markedly from those of Hampson and Weissberger, from which a moment of 1·64 has been recalculated. [d] Næshagen gives 1·44 (*loc. cit.*). [e] Measured in present work (Part I). [f] Næshagen, *loc. cit.* The value of 3·40 given by Syrkin and Dyatkina ("Structure of Molecules," Butterworth, 1950, p. 222) is presumably a misprint. [g] Næshagen (*loc. cit.*) gives 3·79, Le Fèvre and Le Fèvre (*loc. cit.*) 3·80 (recalculated), and Lumbroso (*Bull. Soc. chim.*, 1949, **16**, D387) 3·82. [h] Literature values are: 1·73 (Næshagen, *loc. cit.*), 1·76 (Le Fèvre and Le Fèvre, *loc. cit.*), 1·74 (Kumler and Halverstadt, *J. Amer. Chem. Soc.*, 1941, **63**, 2182), and 1·71 (Bergmann and Weizmann, *Chem. Rev.*, 1941, **29**, 553). Kumler and Halverstadt's measurements are considered the most reliable; recalculation of them gives 1·83. [i] Næshagen, *loc. cit.* [j] Bergmann, *J.*, 1936, 402.

dipole moments of the corresponding benzene derivatives are given also for comparison in the last column. Those relating to chlorodiphenyl have been treated in detail by Hampson and Weissberger, who take into account the effect of induction in the unsubstituted benzene ring (*J. Amer. Chem. Soc.*, 1936, **58**, 2111).

If the conjugated hydrocarbon radical is attached *para* to the other substituent in the first benzene ring, the moment in all cases is increased; if in the *meta*-position, it is hardly changed

(differences $> 0{\cdot}1$); and if in the *ortho*-position, it is decreased. These facts can readily be explained on current theory. Resonance between the radical and the substituent can take place only when they are *ortho* or *para* to one another; and when it occurs, it should lead to an increase in moment of the *p*-substituted compounds (the case of 4-chlorodiphenyl receives separate consideration in Part V). The only effect of *m*-substitution of a conjugated system into a benzene derivative should be an inductive one, and it would be expected to be small.

The decreases brought about by *o*-substitution are, reading down the table, 0·15, 0·20, 0·10, 0·03, 0·54, and 0·24. These are probably partly due to induced moments (Hampson and Weissberger, *loc. cit.*). For the groups considered (except chlorine, which is considered later), the additional resonance involving the *o*-substituted conjugated system will decrease the moment relative to that of the parent benzene derivative because, as it involves a shift of charge from the benzene ring to the *o*-substituted system, the moment to which it gives rise will be partly opposed to the original one. This is indicated in the diagram, where μ_2 clearly has a component antiparallel to the original moment μ_1.



2-Aminostilbene shows an insignificant reduction relatively to aniline, whereas 2-dimethylaminostilbene shows a very large one relatively to dimethylaniline. The difference is too large to attribute to the slight difference in mesomeric effects of the two groups (Table II, Part V, p. 2824); it must be ascribed to the steric inhibition of resonance, such as is found in dimethylmesidine (Ingham and Hampson, *J.*, 1939, 981). Scale models show that this should not occur in 2-aminostilbene, on the other hand.

Twisting of either the dimethylamino-group or the styryl group about the bonds joining them to the benzene ring would relieve the interference, though only incompletely in the latter case. If the styryl group alone twisted through 90°, 2-dimethylaminostilbene would be expected to have much the same moment as dimethylaniline, 1·61. If, on the other hand, the dimethylamino-group twisted, a moment similar to that of the sterically-hindered dimethylmesidine (1·03 : Ingham and Hampson, *loc. cit.*) or 2 : 4 : 6-tribromodimethylaniline (1·05 : Few and Smith, *J.*, 1949, 2663) would be expected. The experimental result, 1·07, shows that the latter process occurs. A similar conclusion has been drawn from the ultra-violet absorption spectrum of the substance (Roe, personal communication).

It is particularly important to establish the coplanarity of the stilbene fragment in this compound for, if it were not coplanar, it would be an exception to the rule (Haddow, Harris, Kon, and Roe, *Phil. Trans.*, 1948, *A*, **241**, 147) that an essential feature of growth-inhibitory properties in stilbene derivatives is the unbroken conjugation of the stilbene system. This compound is active, though less so than the 4-substituted isomer.

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625. *Polarisation in Conjugated Systems. Part IV. Mesomeric Moments.*

By K. B. EVERARD and L. E. SUTTON.

Mesomeric moments are derived for several 4-substituted derivatives of benzene, diphenyl, stilbene, and 1 : 4-diphenylbutadiene. When these are plotted against the lengths of the conjugated systems, a series of straight lines are obtained, the slopes of which are characteristic of the substituents. The closeness of the fit is probably accidental, because the mesomeric moments of styrene derivatives do not fall on the lines.

The mesomeric moments of aniline and 4-aminostilbene agree well with those calculated from Coulson and Jacobs's π-electron distribution diagrams (*J.*, 1949, 1983), obtained by molecular-orbital calculations.

FOR the remaining papers in this series it is necessary to derive values of mesomeric moments, since these pertain more closely to the mobile electron distribution in the conjugated systems examined than do the gross dipole moments. The mesomeric moment (abbreviated to μ_m) of an aromatic compound Ar–X is here defined as the vector difference between its dipole

moment and that of its aliphatic analogue Alk–X (cf. Sutton, *Proc. Roy. Soc.*, 1931, *A*, **133**, 668; *Trans. Faraday Soc.*, 1934, **30**, 789; Marsden and Sutton, *J.*, 1936, 599). A discussion of the reason for this definition and its validity will be given in Part V.

For compounds containing angular groups such as NH_2 (or NMe_2) the direction and magnitude of the σ-bond moment are needed. The former would be available if the nitrogen valency angle in aniline and related compounds were known. No reliable value seems to exist, however, so it is necessary to derive one. For this purpose, the dipole moments of *p*-phenylenediamine and benzidine, and of their *NNN'N'*-tetramethyl derivatives were measured (Part I). It was then assumed (i) that the N–H and N–Me bond moments, the nitrogen valency angle, and the rotational orientation of one group are not affected by the presence of the other group, (ii) that the N–H and N–Me σ-bond moments are the same as in ammonia and trimethylamine (1·31 and 0·86), and (iii) that one-third of the lone-pair dipole can be reckoned as part of each bond moment. It follows that the component of the amino-group moment resolved at right angles to the 1 : 4 diagonal of the ring is $1/\sqrt{2}$ times the moment of *p*-phenylenediamine or benzidine (a general proof of this is given by Everard and Sutton, *J.*, 1951, 16). This component is wholly due to the effective moments of the two N–H bonds. Knowing these, the angles between each of the bonds, and between one of the bonds and the 1 : 4 diagonal, can be calculated vectorially. The same treatment can be applied to the tetramethyl compounds. The value obtained for the nitrogen valency angle is 108—111°, *i.e.*, approximately tetrahedral; but it is rather sensitive to the assumptions made.

It will further be assumed that the bond angles and the σ-bond moments are constant, no matter what is joined to the amino-group. Though these assumptions are crude, they are unlikely to invalidate the conclusions that we shall draw later.

Derivation of the mesomeric moment also requires a knowledge of the direction of the gross moment in the compounds with angular substituents. One way of obtaining this in the specific case of dimethylaniline has been described by Marsden and Sutton (*loc. cit.*): it involved measuring the moment of dimethyl-*p*-toluidine. Owing to the small value of the methyl-substitution moment, this method is rather sensitive to error. Nevertheless, the value that we have recalculated agrees well with that obtained from the moments of the amine and the corresponding *p*-diamine by Hertel and Dumont's method (*Z. physikal. Chem.*, 1935, *B*, **30**, 139) based on the vectorial property that the total moment of each amino-group must be the resultant of those perpendicular to and parallel to the axis of rotation. The former component is found as above (1·13 for NH_2; 0·79 for NMe_2). The latter, and hence the direction of the total moment, then follows.

Similar considerations apply to the acetyl group. The direction of the moment of acetophenone was given as 130° ± 1° to the Ph–Ac bond by Bentley, Everard, Marsden, and Sutton (*J.*, 1949, 2957); this value was obtained from the moments of some *para*-substituted acetophenones. We now obtain 132°, in good agreement, from the moments of acetophenone and *p*-diacetylbenzene.*

The directions of the constituent moments having been established, it is a simple matter to obtain the mesomeric moments. A list of those that will be needed is given in Table I.

TABLE I.

Mesomeric moments of 4-substituted compounds.

	NO_2.	Ac.	CN.	NH_2.	NMe_2.	Br.	Cl.
Benzene	0·76	0·46	0·45	1·02	1·66	0·43	0·41
Styrene †	1·10	—	—	—	2·14	0·33	0·40
Diphenyl	1·16	—	0·73	1·44	2·14	0·35	0·37
Stilbene	1·31	0·61	0·82	1·73	2·54	0·33	—
1 : 4-Diphenylbutadiene	1·50	—	—	—	2·72	—	—

† It is assumed that styrene has a moment of 0·12 (see below).

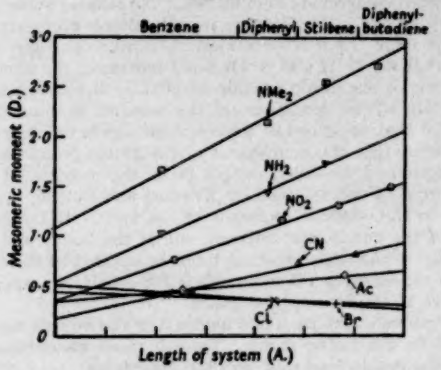
They are based on the dipole moments given in Parts I and III. No distinction is made between electron-releasing and electron-accepting groups; *i.e.*, the direction of μ_m has not been specified.

In order to exhibit the dependence of mesomeric moments on the conjugated systems to which they relate, the former have been plotted against the lengths of the latter from end to

* Weissberger (*J. Amer. Chem. Soc.*, 1945, **67**, 778) gave the moment of *p*-diacetylbenzene as 2·71. A study of his measurements suggests, however, that he made an error in ε_1 of 0·028. The dipole moment has accordingly been recalculated by Halverstadt and Kumler's method, and the revised value of 3·10 obtained.

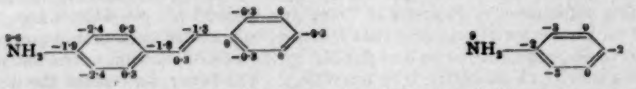
end (Fig. 1). Although we have actually plotted the length, it would doubtless be possible to have taken some other extensive property of the systems, such as their molar volumes or molar refractions. With the lengths, however, a series of straight lines is obtained, the slopes of which are characteristic of the substituent groups. The linear relationship is remarkably

FIG. 1.



exact; the standard deviation of the points from their respective lines (Ac and Cl being omitted) is 0·03 D. It could be explained very simply by supposing that the charge leaving the polarising group is independent of the attached system and is distributed evenly over it. Notwithstanding, two facts point to its being accidental.

FIG. 2.



The net charges on the atoms are shown in units of $-e/100$: i.e., *positive charges are given a positive sign.*

(i) A. Pullman (*Compt. rend.*, 1948, **226**, 486) calculated the π-electron distribution in 4-aminostilbene, and found that, quite apart from alternating polarity effects, the formal charge distribution is very uneven, there being more charge on the β-carbon atom than on the whole of the second benzene ring. Coulson and Jacobs (*J.*, 1949, 1983), using a different method of computation, confirmed this result and also performed calculations on aniline; their results are reproduced in Fig. 2. The pattern of distribution is likely to be similar for other groups.

(ii) The mesomeric moments of styrene derivatives do not lie on the lines through the other points. The discrepancies in the ordinates are shown in Table II, row 1.

TABLE II.

Substituent.	4-NMe_2.	4-NO_2.	4-Cl.	4-Br.	β-NO_2.	β-Ac.	β-Br.	Root mean square.
μ ("obs.") / −μ (interpolated)	0·35	0·01	0·12	0·08	0·33	0·19	−0·02	0·22
Ditto (corrected)...	0·02	0·02	−0·02	0·02	−0·06	−0·02	−0·11	0·03

Three β-substituted styrenes have been included, but we cannot be sure that they should be comparable. The reliability of the measurements on which the values for β-bromo- and β-acetyl-styrene are based is unknown. β-Nitrostyrene, however, has been re-examined recently (Part I).

Better agreement and consistency are obtained, as shown in Table II (row 2), by making two assumptions: (*a*) that styrene itself has a dipole moment, not of zero, but of about 0·12, in such a sense that the vinyl group accepts electrons from the phenyl group (cf. Part I); and (*b*) that the abscissæ for styrene derivatives in Fig. 1 are increased by *ca.* 1·5 A.

The need for increasing the abscissæ of the 4-substituted styrenes would be expected by reference to Fig. 2, if substitution of the second benzene ring in 4-aminostilbene by hydrogen had only a minor effect on the electron distribution in the rest of the system, and, in particular, on the large charge on the β-carbon atom; in this connexion it is noteworthy that the moments of 4-dimethylaminostyrene and of 4-dimethylamino-2′ : 4′ : 6′-trimethylstilbene are similar (2·15 and 2·11), for the second ring in the latter is prevented from conjugating (Part II). The fact that these moments are nearer to that of 4-dimethylaminostilbene (2·41) than to that of dimethylaniline (1·61) supports the view that the charge migrating to the second benzene ring is smaller than that on the β-carbon atom. It must be remembered also that the former charge migrates further than the latter; consequently, the dipole moment to which it gives rise is proportionately, though not actually, greater.

The mesomeric, or π-bond moments of aniline and 4-aminostilbene, may be calculated from the charges given in Fig. 2. They are 1·17 and 1·63, respectively. The observed ones are 1·02 and 1·73. The agreement is much better than that usually obtained in comparisons of this sort (see, *e.g.*, Hill and Sutton, *J.*, 1949, 746; Bentley, Everard, Marsden, and Sutton, *J.*, 1949, 2957; Orgel, Cottrell, Dick, and Sutton, *Trans. Faraday Soc.*, 1951, **47**, 113); and it might be better still, for the charge distributions are not given to sufficient figures to make the last figure of the moments significant. Evidently, Coulson and Jacobs's statement (*loc. cit.*) that " our charge migrations are probably too large," is too conservative. It may be because the charge migrating is so small relative to that in these other cases, that the agreement is so good.

Pullman's charge distributions (see above) lead to a π-bond moment of 4·34 for 4-aminostilbene. It seems that her treatment exaggerates some of the formal charges.

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626. *Polarisation in Conjugated Systems. Part V. The Polar Effect of the Halogens and Other Groups.*

By K. B. EVERARD and L. E. SUTTON.

Theories of interaction between unsaturated hydrocarbon radicals and substituent groups are reviewed, with special reference to the mechanism of the inductive effect. The balance of evidence is in favour of the view that the latter is not altogether a short-range classical electrostatic phenomenon, but that it has a long-range non-classical component which must be explained in wave-mechanical terms.

The polarising effects of the halogens are considered in detail. Both theory and experiment support the view that they form π-bonds with conjugated systems, but this is not thought to be solely responsible for the apparent mesomeric moments (μ_m) in such systems; μ_m values for chlorobenzene and bromobenzene hardly alter when the conjugated system is extended (as in 4-chlorodiphenyl, etc.; see Part IV), which suggests that there is a balance between the mesomeric effect and the non-classical inductive effect beyond the first benzene ring, and probably that the net formal charge at the *para*-position is small. A discussion of how this arises is given.

μ_m is analysed into four terms, depending on: (i) the different electrostatic polarisabilities of the alkyl and aryl radicals used to obtain μ_m, (ii) the different σ-bond moments resulting from the different orbital hybridisation of carbon in these radicals, (iii) the non-classical inductive effect, and (iv) the acceptance or release of π-electrons by the substituent. Terms (iii) and (iv) determine the rate of increase of μ_m with extension of the conjugated system (see Part IV). Term (iv) can be separately evaluated when it is possible to twist the substituent by steric influences, and so prevent it from conjugating. The polarisations produced by certain common groups have been examined in these ways.

THE theory of the interaction of substituent groups with unsaturated hydrocarbon radicals to which they are attached is familiar in its general outlines; and it has been assumed in the

foregoing papers. We must now examine it more critically, however, particularly in its relation to the aryl halides. The language used to discuss the problem has been altered by the introduction of a more nearly deductive and semi-quantitative theory based on wave-mechanics; but the fundamental ideas remain much the same.

It is generally supposed that interaction may occur in two ways: (i) the electric field of the substituent group may polarise the radical (Robinson's and Ingold's *inductive effect*); (ii) the group may form a π-bond with the carbon atom to which it is attached, and this has repercussions on the π-bonds already in the radical (*mesomeric effect*, or formerly *electromeric* or *tautomeric effect*). In slightly different language, it participates in a molecular orbital with the carbon atoms of the radical. Both processes result in a drift of electrons to or from the substituent group, and they may reinforce or oppose each other.

Polarisation by the electric field has been visualised in two ways. On the one hand, it has been regarded purely as a classical electrostatic process, the moments induced in the various parts of the radical being severally equal to the product of the local field and the local polarisability which is assumed to be independent of field strength. If the bonds in the unsaturated radical have the same order and (hence) polarisability, *e.g.*, those in the phenyl radical, the induced moments would fall steadily with distance from the inducing dipole; otherwise, *e.g.*, in the butadienyl radical, there would be fluctuations about the falling mean. In either case, the inductive effect would die down rapidly. Frank (*Proc. Roy. Soc.*, 1935, *A*, **152**, 171) has shown by classical electrostatics that the moment induced at any point is proportional to the inverse cube of its distance from the polarising dipole, so that the inductive effect must be a relatively short-range one. An example of this is the rapid approach of moments to a limiting value as a homologous series of paraffin derivatives is ascended. This view of the inductive effect in conjugated systems has been taken recently by W. C. Price and Walsh (*Proc. Roy. Soc.*, 1947, *A*, **191**, 22).

On the other hand, induced polarisation has been regarded (*e.g.*, by Robinson, by Ingold, and by Wheland and Pauling) as a process involving not only the classical part just described, but also a non-classical part, in which the field of the substituent causes changes of π-bond order, as may be seen, *e.g.*, from the resonance representation of the situation (I). This could affect the whole of the conjugated system in the radical, just as the mesomeric effect does (II). Such "long-range" effects permit an explanation of the proportionality of the mesomeric moments to the length of the system, which was noted in Part IV; whereas the classical inductive effect certainly does not.

(I.) (II.)

The two non-classical effects, unlike the classical one, cause changes of local charge only at alternate atoms, and, because they both act through the same medium (*viz.*, the π-bond system), they are not independent. Moreover, electron distributions in σ- and in π-bonds are not independent either, for a change of local charge in one will affect the other. This will be clearer when the wave-mechanical treatment is considered more fully.

The relationships between the effects are brought out in Table I.

TABLE I.

	Effect.	Medium.	Atoms affected.	Resonance representation.	Range.	Interdependence.
Inductive	Classical	σ and π	All	—	Short	← because changes of local charge in σ-bonds affect associated π-bonds, and *vice versa*.
Inductive	Non-classical	π	Alternate	(I)	Long	← because both act through same medium ←
	Mesomeric	π	Alternate	(II)	Long	←

The Polar Effect of Halogens.—Both Robinson and Ingold suggested that the inductive and mesomeric effects in halogenobenzenes are opposed. The C–X dipole field *reduces* the negative charges on all the atoms in the ring, but especially (by the non-classical polarisation) on the *o*- and *p*-carbon atoms; the mesomeric effect *increases* the negative charge on these latter atoms. In the molecule unperturbed by the approach of a reagent, the differences of charge at the *o*-, *m*-, and *p*-positions are likely to be small; so it might be supposed that there would be little difference in reactivity at the several positions toward cationoid or electrophilic reagents. To overcome this difficulty it was postulated that the reagent could itself polarise the molecule and that the non-classical polarisations which involve conjugation with the

substituent group are more important than those which do not; *i.e.*, there is greater polarisability at the *o*- and *p*-atoms than at the *m*-, so the former positions are predominantly attacked.

Some authors have questioned this explanation, because there is an apparent contradiction in the statements that (i) the halogen atom releases electrons to the hydrocarbon radical by the mesomeric process, and (ii) it pulls them away by the inductive process. Process (i) is particularly implausible when the halogen is fluorine. Baddeley and Bennett (*J.*, 1933, 261) suggested that the carbon–halogen bond dipole produces oppositely directed fields in its own vicinity and in that of the ring. C. C. Price (*Chem. Reviews*, 1941, **29**, 37; "Reactions at Carbon–Carbon Double Bonds," Interscience, 1946, Chap. I) and Leonard and Sutton (*J. Amer. Chem. Soc.*, 1948, **70**, 1564) have expressed similar views.

It might be hoped that the application of wave-mechanics to the problem would resolve such arguments by making a more fundamental discussion possible; but unfortunately a radically different treatment is not practicable. Certain points are, however, clarified. It has been demonstrated that a non-classical inductive process will augment the classical one in a conjugated system if the perturbing field is intense enough; a perturbation treatment (Coulson, Maccoll, and Sutton, to be published) has shown how the classical view breaks down by the development of "hyperpolarisability" in fields of the strength to be expected in the neighbourhood of dipoles and ions.

The origin of the π-electron drifts can be explained; and they can be treated semi-quantitatively by the molecular-orbital method. Molecular orbitals are constructed from two or more atomic π-orbitals, which each contribute to an extent depending on the electron affinity of the atom; so electrons in the molecular orbitals congregate mainly round atoms of high electron affinity, which may therefore be said to polarise the bond system as a whole. In a halogenobenzene, however, because the halogen contributes an already filled π-orbital to the π-bond system, it cannot thereby gain negative charge. On the contrary, it must release some, though the amount may be small because of the high electron affinity (see Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, 1947, *A*, **191**, 56).

The electron affinity of an atom is affected by its environment: that of a carbon atom attached to a halogen, for example, is larger than normal because the $C^+–X^-$ σ-bond dipole gives the carbon atom a positive charge. It also depends upon the π-electron charge on the atom (as well as *vice versa*): if the halogen acquires a positive one, its electron affinity is clearly increased. Finally, the σ-bond dipoles are affected by the π-electron charges around them.

Several interacting, self-adjusting processes ought, therefore, to be considered, but in practice this cannot be done rigorously. What is usually done is to treat σ-bonds and π-bonds separately, and to suppose that the electron affinities are independent of π-electron distribution (see, however, Wheland and Mann, *J. Chem. Physics*, 1949, **17**, 264; Moffit, *Proc. Roy. Soc.*, 1949, *A*, **196**, 510). For the calculations, it is necessary to know the values of two sets of parameters which characterise respectively the atoms and the π-bonds between pairs of atoms, and which both depend upon the electron affinities. Neither set can be obtained *a priori*; both are commonly obtained by adjustment to give consistency in a series of related compounds or to give some desired answer such as that there is a residual negative charge at the *ortho*- and *para*-positions. It is common practice not only to consider the nature of the atom in assigning parameters of the first set, but to take account of its environment; the second set should similarly be adjusted for environment, but here this is less important, and it is not always done.

In the aryl halides the evaluation is particularly difficult because there is so delicate a balance between the mesomeric and non-classical inductive effects. It has proved necessary to add the assumption of the earlier theory, that polarisation by the reagent is a dominant factor; and this has been placed on a sound theoretical footing by Wheland and Pauling (*J. Amer. Chem. Soc.*, 1935, **57**, 2086), Wheland (*ibid.*, 1942, **64**, 900), and Coulson and Longuet-Higgins (*Proc. Roy. Soc.*, 1947, *A*, **192**, 16).

As remarked above, it has been claimed that theory shows definitely the occurrence of π-bonding between the halogen and the radical (*idem*, *ibid.*, 1947, *A*, **191**, 56). Furthermore, two pieces of experimental evidence have a bearing. (i) Price and Walsh (*ibid.*, p. 22) have shown that the ultra-violet absorption spectrum of chlorobenzene is shifted to long wave-lengths relative to that of benzene, and hence that the first ionisation potential of the ring π-electrons in the former (8·77 v.) is lower than it is in the latter (9·24 v.). This indicates a drift of electrons into the ring. The same point is illustrated more strikingly by the decrease of the ionisation potential of benzene to 9·197 v. when fluorine is directly substituted on the ring, in contrast with the increase to 9·683 v. when the polar group CF_3 is substituted (Hammond, Price, Teegan, and Walsh, *Discuss. Faraday Soc.*, to be published). (ii) Goldstein and Bragg (*Physical*

Rev., 1949, **75**, 1453) have suggested that the microwave absorption spectrum of the analogous vinyl chloride can be plausibly interpreted only by postulating multiple bonding between the chlorine atom and the vinyl group.

The general conclusion is that the halogens do form π-bonds with conjugated carbon systems; and the apparent difficulty which is particularly prominent with fluorine, namely, that such bonding appears to be contrary to the electron-attracting character of these substituents, must be met by taking account of the possible gain of electrons through the σ-bond.

It does not appear that the difficulty is disposed of by the revision of the electron affinity of a gaseous fluorine atom by Evans, Warhurst, and Whittle (*J.*, 1950, 1524), who conclude that it is not more than that for chlorine and is very probably less: they remark, in effect, that, because the radius of covalently bound fluorine is small (whatever the cause of this may be), the field around it will be large.

Baddeley (*J.*, 1950, 663) has suggested that the overlap of the π-orbitals may be more favourable in fluorobenzene than in the other halogenobenzenes.

Evidence from Part IV.—In Part IV, values of an experimental quantity called the mesomeric moment were reported. This, being the vector difference between the moments of the aryl and alkyl compounds, should give the moment due to the non-classical polarisations, *i.e.*, to the mesomeric effect together with the non-classical part of the inductive effect. This is denoted as μ_m. It must, however, include also any error in allowing for the classical polarisation, and any non-compensating alterations in the C–X and C–H σ-bond moments due to change in the effective electronegativity or atomic radius of carbon when its hybridisation changes from sp^3 to sp^2. The importance of the latter effect has been suggested by Branch and Calvin ("Theory of Organic Chemistry," Prentice-Hall, 1941, p. 147) and by Walsh (*J.*, 1948, 398).

We saw in Part IV that when the apparent mesomeric moments, μ_m, of *p*-substituted aromatic systems are plotted against the lengths, *l*, of the systems, straight lines are obtained (Fig. 1, Part IV), the slopes of which ($d|\mu_m|/dl$) are characteristic of the polarising substituent (Table II, row 1).

TABLE II.

	NMe_2.	NH_2.	NO_2.	CN.	Ac.	Br.	Cl.
$d\|\mu_m\|/dl$	0·13	0·11	0·08$_5$	0·05$_6$	0·02$_3$	−0·01$_8$	−0·01$_1$
$d\|\mu_m\|/dl$ (corr.)	0·13	0·11	0·07$_0$	0·04$_4$	0·02$_3$	−0·00$_3$	+0·01$_1$

No distinction is made between electron-releasing and electron-accepting substituents, because the modulus, $|\mu_m|$, not μ_m, is taken.

It will be noticed that the halide series are exceptional, inasmuch as their mesomeric moments decrease in magnitude with extension of the system, whereas those of all the other groups increase. One possible explanation of this is the neglect of moments induced by the C–X dipole in the system beyond the first benzene ring (see above). Any error in allowing for the moment induced in the latter by the primary dipole is, however, at least common to all μ_m values in the series; so the only relevance of this induced moment is its secondary induction of a moment in the "tail," which is negligible. The moment *directly* induced in the latter by the C–X dipole is, however, just appreciable. Values for some compounds in the series have already been calculated by Le Fèvre and Le Fèvre (*J.*, 1936, 1116); their procedure has been followed, except that the polarising dipole has been taken as that of the appropriate group, and not that of the whole molecule. When these corrections for induction are applied, it is found that the changes in $d|\mu_m|/dl$ are quite small (see above table, row 2).

Two questions have therefore to be answered: (i) Why is $d|\mu_m|/dl \approx 0$ for the halogens? (ii) That being so, why is $\mu_m \neq 0$, *i.e.*, why is the moment of an aryl halide different from that of an alkyl halide?

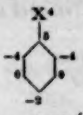
The first question may be re-phrased: Why is there no long-range polarisation in the aryl halides? To this, the most probable answer is that the mesomeric effect and the non-classical inductive effect, which would be opposed in the aryl halides, nearly cancel beyond the first benzene ring. This does not necessarily mean that the net moment due to non-classical π-electron rearrangements in the fragment $X{\cdot}C_6H_4{\cdot}$ is zero, because the systems involved in the two effects are different (formulæ I and II); but it is likely to be small. It probably means that the net formal charge at the *p*-position is very small. That such a condition could actually arise from an accidental relation between the electron affinity parameters, δ, defined by Wheland and Pauling (*loc. cit.*), and that this relation is a possible one, may be seen from Fig. 1, based on two sets of parameters which they considered. It appears that μ_m could be small and

its direction uncertain; likewise, that the charge on the *p*-position could be very small and its sign indeterminate. These calculations require extension to stilbene and diphenyl compounds. Also, since it is, of course, unlikely that $d|\mu_m|/dI$ would be so near zero for all the halogens, it would be of great interest to obtain values for the full series of fluoro- and iodo-compounds.

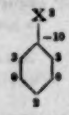
FIG. 1.

Electron distribution in a halogenobenzene (in units of $-e/100$; i.e., positive charges are given positive signs).

(*a*) $\delta_X = 4$; all other δ values = 0. (*b*) $\delta_X = 4$; $\delta_1 = 0{\cdot}4$.



$\mu_m = +0{\cdot}86$ (↕).



$\mu_m = -0{\cdot}22$ (↕).

If this hypothesis be correct, we must conclude that the reason why $\mu_m \neq 0$ is that there may be some contribution from π-electron rearrangement (though less than is commonly supposed), some error in allowing for classical polarisation, and some effect due to change of hybridisation of the carbon atom, and possibly also of the halogen atom. It has been argued that sp^2-hybridised carbon has a higher electronegativity than has sp^3-hybridised carbon (Walsh, *loc. cit.*), which would make the C–X σ-bond dipole smaller in aryl than in alkyl compounds. Against this must be set the effect of the formal charges on the carbon and halogen atoms due to π-electron rearrangement, which are such as to increase the σ-bond moment.

The Polar Effects of Other Groups.—If the conjectures in the preceding section are correct, the " mesomeric moment " of any compound (as defined in Part IV) can be analysed into four terms, which depend on, respectively:

(i) the different classical electrostatic polarisabilities of the saturated and the aromatic radicals which are used to obtain μ_m;

(ii) the different C–X and C–H σ-bond moments in the saturated and the aromatic compounds;

(iii) the non-classical inductive effect; and

(iv) the mesomeric effect proper, *i.e.*, the acceptance or release of π-electrons by the substituent.

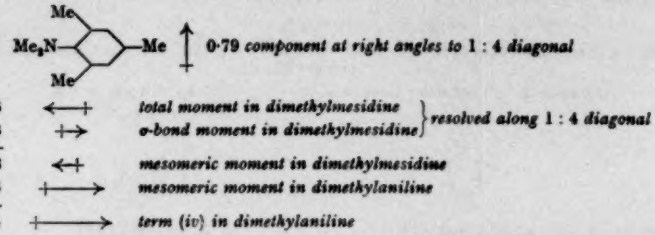
The quantity $d|\mu_m|/dI$ measures the effect of terms (i), (iii), and (iv) only; and when a correction is made for induction, as in Table II (row 2), the effect of (i) is eliminated also. It is therefore a truer measure of the π-bond polarising power of the substituent than is the mesomeric moment.

Term (iv) can be separately evaluated in compounds with a substituent which can be twisted at right angles to the plane of the aromatic system, by steric blocking. The moment of nitrodurene, for example (3·62; Kofod and Sutton, unpublished), unlike that of nitrobenzene (4·01), does not include any contribution from term (iv), because the nitro-group cannot conjugate with the ring. Since the sum of the induced dipoles in the methyl groups vanishes (Birtles and Hampson, *J.*, 1937, 10), the difference (0·39) between these two moments must represent term (iv) in nitrobenzene; *i.e.*, it represents the ability of a nitro-group to accept π-electrons from a phenyl radical. If the conjugation is not completely inhibited, this value would be a lower limit.

The same treatment can be applied to dimethylmesidine ($\mu = 1{\cdot}03$; Ingham and Hampson, *J.*, 1939, 981), for which spectroscopic data indicate that conjugation is entirely inhibited (Klevens and Platt, *J. Amer. Chem. Soc.*, 1949, **71**, 1714). A difficulty arises in that the sense of the total moment is not obvious, *i.e.*, whether the negative or the positive pole is directed away from the ring. However, the ambiguity can be resolved by using the moment of dimethyl-2:6-xylidine (0·94; Fischer, *Acta Chem. Scand.*, 1950, **4**, 1197). This sterically hindered compound differs from dimethylmesidine in having an extra moment of 0·35 (the moment of toluene or *m*-xylene) directed along the 1:4-diagonal with its negative end away from the NMe_2 group. The component of the moment of dimethylmesidine resolved at right angles to the 1:4 diagonal is found to be 0·79 (from the moment of tetramethyl-*p*-phenylenediamine); so the component along the diagonal must be $\sqrt{(1{\cdot}03^2 - 0{\cdot}79^2)} = \pm 0{\cdot}66$. From these, and the moment of toluene, we can calculate two alternative values for the moment of dimethyl-

2 : 6-xylidine, *viz.*, 1·28 and 0·85. The latter, from −0·66, agrees with the observed value of 0·94, showing that the moment along the 1 : 4 diagonal in dimethylmesidine has its negative

FIG. 2.



pole towards the NMe_2 group (Fig. 2). Hence, by taking away the σ-bond moment (see Part IV), the mesomeric moment is $-0{\cdot}66 + 0{\cdot}28 = -0{\cdot}38$, *i.e.*, also towards the NMe_2 group, and in the *opposite* direction to that in dimethylaniline (+1·66).

This result might have been expected because, although in dimethylmesidine term (iv) of the mesomeric moment is eliminated, yet term (iii), which opposes it, remains. Evidently, term (iv) in dimethylaniline is $1{\cdot}66 + 0{\cdot}38 = 2{\cdot}04$.

If it can be assumed that the mesomeric moment of a hypothetical aniline molecule in which the amino-group does not conjugate with the ring is also 0·38, then term (iv) in aniline is only 1·40. This quantity cannot be obtained except by analogy, because the *N*-hydrogen atoms in mesidine are not big enough to suppress, by their interference with the *o*-methyl groups, the conjugation of the amino-group with the ring. Nevertheless, the conclusion that nitrogen parts more easily with π-electrons when it has two methyl groups attached than when it has two hydrogen atoms is almost certainly correct; and the moment of 4-diethylaminostilbene (2·69) compared with those of diethylaniline (1·65; Krasil'nikov, *J. Phys. Chem. U.S.S.R.*, 1944, **18**, 174: 1·81; Barclay, Le Fèvre, and Smythe, *Trans. Faraday Soc.*, 1951, **47**, 357), dimethylaminostilbene (2·41), and dimethyl aniline (1·61), suggests that with ethyl groups the effect is still greater. It should therefore be clear that in molecular-orbital treatments of conjugated molecules it is not legitimate, unless the treatments are to be unnecessarily rough, to consider electron affinity parameters as characteristic solely of the atoms concerned; they must depend quite markedly on whether the atoms bear hydrogen or alkyl groups, and allowance should be made for this (cf. Orgel, Cottrell, Dick, and Sutton, *Trans. Faraday Soc.*, 1951, **47**, 113).

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627. *Polarisation in Conjugated Systems. Part VI. Interaction Moments and Related Topics.*

By K. B. EVERARD and L. E. SUTTON.

The interaction moments of a given pair of groups are smaller in stilbene and diphenyl than in benzene derivatives; possible reasons are given.

From the dipole moment of *cis*-4-bromo-4′-nitrostilbene, in which there is shown to be considerable steric inhibition of conjugation, it is calculated that the C=C–C valency angle at the ethylene bridge in the molecule is 131°.

The discrepancy between the observed and calculated moments of 2-chloro-4′-dimethylaminostilbene suggests that the central C=C bond may be unusually polar, which can be correlated with the pronounced nucleotoxic properties of the compound.

THE term " interaction moment " has been used by Marsden and Sutton (*J.*, 1936, 599) to mean the difference between the observed moment of a *para*-disubstituted benzene derivative and the algebraic sum of the moments of the two corresponding monosubstituted compounds.

In the case of angular substituents like NH_2, however, a vector treatment has to be employed, and it is assumed that the interaction moment acts along the 1 : 4 diagonal of the ring.

These authors and Leonard and Sutton (*J. Amer. Chem. Soc.*, 1948, **70**, 1564) have published tables of interaction moments in benzene derivatives, but few other systems have been studied. For certain compounds, no reliable moment value exists; therefore those interaction moments which have been based on unreliable values need correction.

Although relatively few of the compounds examined in the present work (Part I) are relevant to this topic, they suffice to demonstrate one important point. The available values are collected in Table II, and are based on the dipole moments listed in Table I.

TABLE I.

Dipole moments of p-*disubstituted compounds.*

	NMe_2. Cl.	NH_2. Br.	NO_2. Br.	NO_2. NMe_2.	NO_2. NH_2.
Benzene	3·32 [a]	2·87 [b]	2·68 [c]	6·87 [a]	6·35 [b]
Diphenyl	—	3·30 [b]	—	—	6·49 [b]
Stilbene	4·02 [d]	3·56 [d]	3·11 [d]	7·42 [d]	—

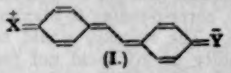
TABLE II.[e]

Interaction moments in p-*disubstituted compounds.*

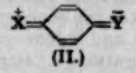
Benzene	0·22	0·05	0·24	1·41	1·22
Diphenyl	—	0·01	—	—	0·54
Stilbene	0·01 [f]	−0·02	0·22	0·54	—

[a] Marsden and Sutton (*loc. cit.*), recalculated. [b] Le Fèvre and Le Fèvre (*J.*, 1936, 1130), recalculated. [c] Saxby, private communication. [d] Part I. [e] See Table I for headings. [f] Mesomeric moment of 4-chlorostilbene estimated to be 0·34 (by extrapolation of Fig. 1, Part IV).

It is clear that interaction moments in diphenyl and stilbene derivatives are usually much less than those in benzene derivatives. Kumler and Halverstadt remarked on the same thing when they measured the dipole moments of sulphanilamide and 4-*p*-aminophenylbenzenesulphonamide (*J. Amer. Chem. Soc.*, 1941, **63**, 2182). Calculation shows that mutual electrostatic induction of moments in each substituent must be small ($\gtrsim -0{\cdot}1$) and sometimes opposed;



(I.)



(II.)

so evidently structures such as (I) contribute less to the resonance hybrids of stilbene (and similarly for diphenyl) derivatives than those such as (II) to the hybrids of benzene derivatives. The phenomenon is the more marked, because structure (I) has about twice the moment of (II). In the case of stilbene, this seems to be another example of the "insulating" effect of the bond between the β-carbon atom and the second benzene ring, which shows up in the electron-distribution diagram given in Part IV (Fig. 2). In the case of diphenyl, it might be a result of the partial suppression of conjugation across the central C–C bond by twisting of the phenyl groups with respect to one another; Bastiansen claims to have shown that the ring planes in certain diphenyl derivatives are inclined at an angle of *ca.* 50° (*Acta Chem. Scand.*, 1949, **3**, 408).

4-Bromo-4′-nitrostilbene.—The interaction moment in *trans*-4-bromo-4′-nitrostilbene is not very large (0·22); but it is curious. The reason for its equality to that in the benzene compound is not clear.

In the *cis*-isomer, the optical evidence reported in Part I shows that conjugation is suppressed; the molar exaltations of the two isomers are 7·4 and 1·8 c.c., respectively, each value having been based on the refraction of the appropriate stilbene isomer. This can be ascribed to steric hindrance (for a photograph of a model, see Wooster, McGowan, and Moore, *J. Sci. Instr.*, 1949, **26**, 140).

Presumably, therefore, any calculation of the moment of the *cis*-isomer should be made with values appropriate for *cis*-bromo- and -nitro-stilbene. If conjugation were inhibited completely, and if there were no interaction, the dipole moments of bromo- and nitro-benzene might be regarded as reasonable estimates. When these are taken, in order to obtain the observed dipole moment of 4·52 for *cis*-4-bromo-4′-nitrostilbene, a value of 82° has to be assumed for the angle between the 1 : 4 and 1′ : 4′ diagonals. This corresponds to a C–$\widehat{C{=}C}$

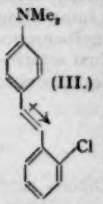
valency angle at the ethylene bridge of 131°. Had the normal trigonal angle of 120° been taken, the calculated moment would have been 0·5 too large. Any increase in the individual Br or NO_2 group moments over the values chosen above (*i.e.*, use of values nearer to those of the *trans*-compounds) would give an even larger angle.

This estimate of 131° may be compared with the 128—133° found by *X*-ray diffraction investigation of the structure of *trans*-stilbene (Robertson and Woodward, *Proc. Roy. Soc.*, 1937, *A*, **162**, 568); *cis*-stilbene itself appears not to have been examined. The prising open of the valencies may be ascribed to steric causes.

2-Chloro-4′-dimethylaminostilbene.—This compound was examined partly to test the assumptions which have to be made in calculating vectorially its moment (hereafter denoted as μ_1) from those of 4-dimethylaminostilbene (μ_2) and 2-chlorostilbene (μ_3). They are: (i) that the rotational orientation of the NMe_2 group is unaffected by the presence of the chlorine atom, (ii) that the direction of μ_2 is correctly determined by the procedure outlined in Part IV, (iii) that μ_3 (which has not been measured) may be correctly estimated from the table in Part III (p. 2817) to lie between 1·45 and 1·60, and (iv) that μ_3 acts along the C–Cl bond.

The result of the calculation is 2·16—2·18, which disagrees with the observed value of 2·65. It is unlikely that the discrepancy arises from an interaction moment, because the insulating effect evident in 4-chloro-4′-dimethylaminostilbene (see Table II) probably extends to its 2-chloro-isomer. Neither could it arise from steric interference by the chlorine atom, which is in any case shown to be absent by the optical evidence (Part II). Since it is also very unlikely that assumptions (i) and (iii) are seriously invalid, we shall confine our attention to (ii) and (iv) which, furthermore, are of particular relevance and importance to the discussion in earlier Parts of this series.

There are two possible ways in which (ii) could be wrong. (*a*) The rotating part of μ_2 (*i.e.*, the component of the NMe_2 group moment at right angles to the C–NMe_2 bond) may not have the value of 0·79 deduced by the method described in Part IV. However, variation of this between 0 and 1 only alters the calculated value of μ_1 by 0·07. (*b*) The non-rotating part of μ_2 may not act along the direction of the C–NMe_2 bond, as has been assumed hitherto. However, it could not possibly be displaced from this direction by more than 9°, corresponding to a π-electron migration along the line joining the nitrogen to the β-carbon atom, and very probably the actual displacement is less than half this (deduced from Fig. 2, Part IV). Displacement through 9° would increase μ_1 only to 2·36 in the configuration shown in (III), corresponding to maximum conjugation energy and minimum steric interference. The increase would be less in other configurations. Clearly, therefore, invalidity of (ii) could not itself account for the difference from μ_1 (observed), though it would help.



(III.)

The other possibility is that the direction of μ_3 is not along the C–Cl bond. A displacement of *ca.* 20° would be necessary to raise the calculated moment of configuration (III) to 2·65. Classical polarisation could not account for this; but non-classical inductive polarisation of the ethylene bridge by the chlorine atom (as shown in III) could do so. It would enhance the polarisation of the bridge caused by the dimethylamino-group.

Summarising Remarks.—Butler has recently suggested that nucleotoxic properties may arise from the presence of a highly polar C=C bond in a molecule (*Nature*, 1950, **166**, 18); and, while due caution must be observed in any attempts to correlate pharmacological action with structure, it may be remarked that our experimental results support the theoretical conclusions of A. Pullman and of Coulson and Jacobs (see Part IV) that such a bond exists in the nucleotoxic 4-dimethylaminostilbene and its derivatives. For lack of suitable material, we have not been able to show that this polarity vanishes when the ethylene bridge is twisted out of the plane of the substituted benzene ring; but we have been able to confirm that conjugation with the second ring is inhibited to a greater or less degree by bulky 2′- or 6′-substituents.

Chlorine in the 2′-position appears to augment the polarity of the bridge bond, as we have seen; and it is noteworthy that the compound is the sixth most potent growth-inhibitor in the large number (*ca.* 120) of compounds examined by Haddow, Harris, Kon, and Roe (*Phil. Trans.*, 1948, *A*, **241**, 147).

The authors gratefully acknowledge the co-operation of the late Prof. G. A. R. Kon, Dr. E. M. F. Roe, and their colleagues at the Chester Beatty Research Institute. They are also indebted to Imperial Chemical Industries Limited for a grant towards the cost of apparatus, and to the Department of Scientific and Industrial Research for a Maintenance Allowance to one of them (K. B. E.).

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628. *The Liquid Dinitrogen Tetroxide Solvent System. Part VII.* Products of Reaction of Zinc with Liquid Dinitrogen Tetroxide.*

By C. C. Addison, J. Lewis, and R. Thompson.

The reaction between zinc and liquid dinitrogen tetroxide involves the evolution of nitric oxide, and the formation of a compound insoluble in the tetroxide having the empirical formula $Zn(NO_3)_2,2N_2O_4$. The action of heat on this compound, and its reactions with organic solvents (particularly ethyl ether) are considered in the light of possible structures for the compound. Heating at 100° results in the removal of the two molecules of dinitrogen tetroxide, leaving zinc nitrate in the pure anhydrous form. This method of preparation is simpler than methods previously described. Zinc nitrate is stable at 100°, but decomposes slowly in the temperature range 100—240°, and rapidly above 240°.

In Part I (*J.*, 1949, S 211), reactions between metals and liquid dinitrogen tetroxide (and solutions of "acids" and "bases" in this medium) have been shown to be analogous, in some respects, to the corresponding reactions involving water or liquid ammonia. A range of metals is under consideration from this point of view, and the reactions with zinc are now described. Reaction between certain metals and liquid dinitrogen tetroxide provides a suitable method for the preparation of anhydrous nitrates which may be difficult to prepare in aqueous medium, and the preparation of anhydrous zinc nitrate is a suitable example of this method.

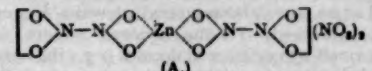
It was stated in Part I (*loc. cit.*) that in contact with liquid dinitrogen tetroxide, "zinc develops a coating of nitrate after about 20 hours"; the surface was then given no preliminary treatment before reaction, and the temperature of the reaction was controlled at 0°. It has been found that if the zinc is cast to a block, so that a fresh surface can be produced by filing, and if the reaction is carried out at a higher temperature, reaction is much more rapid. (Reaction rates are discussed in more detail in the following paper.)

When a block of zinc having a freshly filed surface was added to liquid dinitrogen tetroxide at about 20°, a slight evolution of nitric oxide occurred immediately. After about 10 minutes the metal was covered by a thin layer of white, finely crystalline solid, and the liquid immediately in contact with the metal was coloured green by dinitrogen trioxide. As the crystalline coating became thicker, the crystals were more clearly defined, and about 1 g. of product was formed after 24 hours, and was readily separated from the zinc block. As with other heterogeneous reactions, the yield may be increased by increasing the surface area; by using zinc dust the same yield may be obtained within a few minutes. However, this method of preparation was not used, since it was difficult to confirm that the product was not contaminated with unreacted zinc.

When the dinitrogen tetroxide was allowed to evaporate at a temperature slightly below its boiling point (21·3°), the product was obtained as a free-flowing finely crystalline powder, which was stable for long periods (in a stoppered tube) provided that the atmosphere of dinitrogen tetroxide was maintained. (If this atmosphere was removed, either by evacuating the vessel, or by blowing out the dinitrogen tetroxide with a stream of dry nitrogen, the crystals rapidly decomposed to a pale yellow, viscous liquid.) When the original product was heated, dinitrogen tetroxide was evolved, leaving anhydrous zinc nitrate. Two molecules of tetroxide were originally present for each molecule of zinc nitrate, so the reaction may be represented as follows:

$$Zn + 4N_2O_4 = 2NO + Zn(NO_3)_2,2N_2O_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

This product can be formulated in three ways, (A), (B), and (C). In a compound having structure (A) the N_2O_4 molecules may be regarded as "N_2O_4 of crystallisation"; as in the



(A.)

$(NO^+)_2[Zn(NO_3)_4]^{2-}$ (B.)

$(NO_2^+)_2[Zn(NO_3)_2(NO_3)_2]^{2-}$ (C.)

analogous case of salts containing water of crystallisation, some or all of the N_2O_4 molecules may be associated with the metal ion in the crystal lattice. Bonding is likely to be weak, so the

* Part VI, *J.*, 1951, 1303.

compound should show the properties of both zinc nitrate and dinitrogen tetroxide. In a compound having structure (B), the ion $[Zn(NO_3)_4]^{2-}$ is analogous to the ion $[Zn(OH)_4]^{2-}$ and $[Zn(NH_3)_4]^{2+}$ in the aqueous and the liquid ammonia system, respectively. As dinitrogen tetroxide is no longer present as such, the compound may be expected to exhibit chemical properties differing from either the tetroxide or zinc nitrate alone, although thermal decomposition of the compound should still result in evolution of dinitrogen tetroxide. Relatively few co-ordination complexes containing four or more nitrate groups are known, although a group of compounds of formula $M^1_2[M^2(NO_3)_6]$, where M^1 = Cs, Rb, Tl, or K, and M^2 = Pu, Th, or Ce, have recently been discussed (see Lister, *Quart. Reviews*, 1950, **4**, 37) and these compounds are considered to contain the complex anion $[M^2(NO_3)_6]^{2-}$. Structure (C), although less probable than (B), is analogous to (B), in that it involves the alternative mode of ionisation of the N_2O_4 molecules.

The compound is quite insoluble in liquid dinitrogen tetroxide, and is only rendered soluble by the addition of other compounds (such as alkylammonium salts or diethylnitrosamine) whose presence will result in further chemical reaction, so it is not possible to employ conductimetric or electrolytic methods to differentiate between these structures.* An attempt has been made to electrolyse the viscous liquid which results when part of the dinitrogen tetroxide is removed from the compound. Preliminary experiments indicate that the liquid has a low electrical conductivity, and no electrode effects were observed when electrolysis between Nichrome wires (placed 3 mm. apart) was continued for 30 hours at 250 v. potential difference. It is hoped, later, to obtain evidence of structure by crystallographic methods. However, the following properties of the compound may now be considered in the light of these possible structures.

(1) *Action of Heat.*—The tube containing the white solid was fitted with a phosphoric oxide guard tube (to maintain atmospheric pressure in the tube), and its temperature increased slowly. Decomposition proceeded in the following stages:

(*a*) When dinitrogen tetroxide vapour was allowed to leak from the guard tube, the solid (at a temperature about 15°) changed from free-flowing crystals to a pasty mass in about 2 hours and to a pale yellow viscous liquid after 2 days.

(*b*) The change from solid to liquid was accelerated by slight increase in temperature, being complete within a few minutes at about 25°. The removal of not more than 10% of the available dinitrogen tetroxide resulted in the complete conversion of solid into liquid. This phase change may arise from the depression of the freezing point of the original compound by the zinc nitrate produced, but the considerable degree of supercooling shown by the liquid has prevented the preparation of the relevant phase diagram.

(*c*) On further heating, the liquid continued to lose dinitrogen tetroxide vapour. The mode of decomposition indicates that the reaction

$$Zn(NO_3)_2.2N_2O_4 \rightleftharpoons Zn(NO_3)_2 + 2N_2O_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

is reversible, for on keeping the temperature of the liquid at (say) 40°, evolution of dinitrogen tetroxide appeared to cease after some hours, although the liquid still contained 60—70% of the compound $Zn(NO_3)_2.2N_2O_4$. On reduction of the temperature by 10—15°, dinitrogen tetroxide vapour was reabsorbed by the liquid.

(*d*) Complete removal of dinitrogen tetroxide required about 6 hours at 100°; the slow conversion arises mainly from the slow rate of release of the tetroxide from the viscous liquid. The rate of removal of the last traces of tetroxide could be increased somewhat by heating the liquid under reduced pressure or at a higher temperature, but temperatures appreciably above 100° are undesirable because of the danger of decomposition of the zinc nitrate to zinc oxide.

The behaviour of the compound $Zn(NO_3)_2.2N_2O_4$ on heating clearly does not direct emphasis towards any particular structure. It is significant, however, that during the heating the equilibrium between zinc nitrate and its compound with dinitrogen tetroxide was maintained at all temperatures; the position of this equilibrium appeared to be adjusted smoothly with change in temperature, and at no particular temperature was a pronounced change in the rate of evolution of the tetroxide observed. In the aqueous system, this type of behaviour is characteristic of hydrates formed by complex molecules (*e.g.*, the heteropoly-acids) in which the number of water molecules is large and variable, rather than of salt hydrates containing a small and integral number of water molecules. On the basis of such an analogy, structure (A) above would appear less probable than (B) or (C). In order to confirm that the reaction given in equation (2) proceeds completely in the reverse as well as the forward direction, pure zinc

* The compound dissolves in nitromethane to give a conducting solution; experiments being carried out to determine the nature of the dissociation (or decomposition) will be described in a later paper.

nitrate (prepared as described above) was treated with excess of liquid dinitrogen tetroxide. The white powder was converted almost immediately into a pasty mass, and conversion into clear crystals of $Zn(NO_3)_2.2N_2O_4$ was complete within 20 hours. When a similar reaction was attempted with anhydrous sodium or calcium nitrate, these salts were recovered unchanged when the excess of tetroxide was removed. In structures (B) and (C) the zinc atom occurs in an anionic co-ordination complex, and it is noteworthy that when the zinc nitrate is replaced by the nitrate of a metal which is unable to form such complexes, no combination with dinitrogen tetroxide occurs.

(2) *Action of Organic Solvents.*—A significant reaction occurs between the compound $Zn(NO_3)_2.2N_2O_4$ and dry ethyl ether. At about −5°, no reaction takes place; when warmed, a reaction commences which becomes vigorous at about 20°, and the temperature rises rapidly to the boiling point of the ether. The issuing ether vapour was shown to contain an appreciable quantity of acetaldehyde (but no formaldehyde), as well as dinitrogen tetroxide. On cooling, the liquid phase was found to contain acetic acid, acetaldehyde, and ether, with a little dissolved zinc nitrate. No nitrite was present in the liquid. The solid phase consisted almost entirely of zinc oxide, with only a trace of zinc nitrate. For comparison, both pure zinc nitrate and liquid dinitrogen tetroxide were treated separately with ethyl ether. No reaction whatever occurred with the nitrate, but the tetroxide caused slight oxidation of the ether; this reaction, however, occurred at a scarcely detectable rate.

The reaction of the compound with ethyl ether is therefore quite different in character from that of its two components. This is not consistent with the " hydrate " type of structure (A); on the other hand, a compound having structure (B) would be expected to display chemical properties differing widely from the sum of the properties of zinc nitrate and dinitrogen tetroxide considered separately. Again, anhydrous calcium nitrate, dinitrogen tetroxide, and ether show no appreciable reaction when mixed together, so reaction with ether is not a general property of metal nitrate–dinitrogen tetroxide mixtures. The fact that the solid product of reaction consists almost entirely of zinc oxide supports the belief that the type of bonding between the zinc atom and the nitrate groups is different from that occurring in the normal salt. Any breakdown of the $[Zn(NO_3)_4]^{2-}$ complex (structure B) under these conditions may well be expected to lead to removal of all the nitrate groups.

No reaction takes place between the compound and chloroform, carbon tetrachloride, or benzene. On addition of (say) benzene to the crystals, the benzene layer becomes coloured by dinitrogen tetroxide, and the crystals change to a pasty mass. After a few hours a state of equilibrium is reached; the addition of benzene is therefore equivalent to the application of reduced pressure to the crystals, and repeated treatment with fresh benzene can ultimately convert the crystals into pure zinc nitrate. This process is reversible: when dinitrogen tetroxide is added to benzene containing crystals of zinc nitrate, the latter change to the pasty mass typical of the $Zn(NO_3)_2$–$Zn(NO_3)_2.2N_2O_4$ mixture. The behaviour of the compound with chloroform and carbon tetrachloride is similar to that with benzene. These reactions, considered alone, are of the type to be expected of a compound containing " N_2O_4 of crystallisation " (structure A), and are not readily correlated with the reaction of the compound with ether.

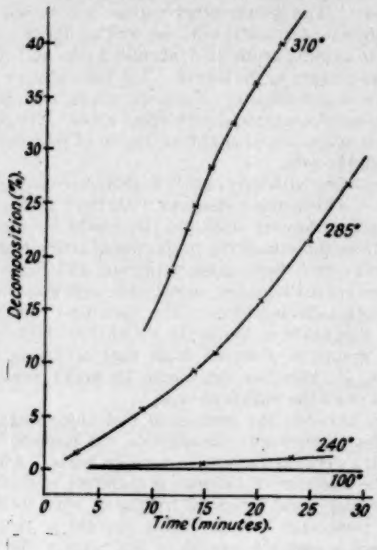
Zinc Nitrate.—The anhydrous salt cannot be prepared from the hydrate, since removal of water of crystallisation leads to decomposition of the nitrate, and the formation of basic salts (Marketos, *Compt. rend.*, 1912, **155**, 210; Dubsky and Nevralova, *Chem. Listy*, 1931, **25**, 373). Marketos (*loc. cit.*) prepared the anhydrous nitrate by heating the tri- and tetra-hydrate at 130—135° in a current of carbon dioxide and dinitrogen pentoxide; a pasty substance was obtained which crystallised on cooling, and commenced to decompose at temperatures slightly above 135°. Ewing, Bradner, and Guyer (*J. Amer. Chem. Soc.*, 1939, **61**, 260) found that " the preparation of anhydrous zinc nitrate offered extreme difficulties." They prepared the material by reaction of gaseous dinitrogen pentoxide with zinc oxide, using ozone to inhibit the slow decomposition of the dinitrogen pentoxide. It is relevant that the compound $Zn(NO_3)_2.2N_2O_4$, and thus anhydrous zinc nitrate, may also be prepared rapidly from zinc oxide and liquid dinitrogen tetroxide: $ZnO + 4N_2O_4 = Zn(NO_3)_2.2N_2O_4 + N_2O_3$. Jander and Wendt (*Z. anorg. Chem.*, 1949, **258**, 1) were able to prepare anhydrous zinc nitrate from zinc picrate and absolute nitric acid. The method of preparation described in this paper is considered to be much more convenient than the methods referred to above, and to give a product which is quite pure.

In order to obtain information on the rate of decomposition of zinc nitrate, samples were heated at various temperatures within the range 100—310°, and the rates of decomposition are

shown in the figure. Zinc nitrate was found to be stable at 100°, and this temperature was employed for its preparation. Very slight decomposition occurred at 150°, but even at 240°, measurements over a longer time range than is shown in the figure indicated that decomposition did not exceed 2% per hour. Above 240°, the rate of decomposition increased rapidly, as indicated in the figure. The quantity of nitrogen dioxide evolved, and the corresponding loss in weight of zinc nitrate, were in accord with the equation $2Zn(NO_3)_2 = 2ZnO + 4NO_2 + O_2$.

Measurements of decomposition rates, over temperature ranges narrower than in the experiments described above, are in hand to determine whether intermediate compounds between zinc nitrate and zinc oxide are formed during decomposition.

Rate of decomposition of zinc nitrate.



Experimental.

Analysis of Product.—A rectangular block of zinc, weighing about 5 g., was suspended in about 10 ml. of liquid dinitrogen tetroxide by means of a glass hook, which passed through a small hole bored in the zinc block. The whole was contained in a glass tube about 3 cm. long, fitted with a B19 ground joint and a phosphoric oxide guard tube. When a quantity (about 1—3 g.) of product had formed, the zinc block was quickly removed by means of the glass rod and hook, and the excess of liquid tetroxide allowed to evaporate at room temperature (about 20°). The tube and contents were then weighed. By preparing the crystals in a short tube with an internal volume of only 12 ml. (approx.) weighing errors due to the atmosphere of tetroxide were reduced to negligible proportions. Great care was necessary to ensure that the product as weighed was in a pure state. Two methods of analysis were used.

(a) *Ignition.* The product was heated at 100—120° until evolution of tetroxide ceased. The nitrate was then ignited to zinc oxide, and from the weight of oxide the zinc content of the original substance, and the zinc nitrate, was calculated :

Expt. no. :	1	2	3	4
Zn, %, in original *product* *	17·5	17·5	17·6	17·5
Zn, %, in intermediate product †	34·7	34·5	35·1	34·6

* $Zn(NO_3)_2.2N_2O_4$ requires Zn, 17·5%. † Calc. for $Zn(NO_3)_2$: Zn, 34·5%.

Since nitric oxide is produced in the zinc–dinitrogen tetroxide reaction, the possibility existed that the original product may contain molecules of N_2O_3 rather than N_2O_4. However, the zinc contents of $Zn(NO_3)_2.N_2O_3$, $N_2O_3.N_2O_4$ and $Zn(NO_3)_2.2N_2O_3$ are 18·29 and 19·15%, respectively, and the experimental results in the above table exclude this possibility.

(b) *Determination of dinitrogen tetroxide evolved.* 1·257 g. of crystals were heated to the zinc nitrate stage in a tube fitted with a trap containing potassium hydroxide pellets, and calcium oxide to absorb

moisture produced in the reaction between the potassium hydroxide and the tetroxide. The weight of tetroxide evolved (determined from increase in the weight of the trap) was 0·620 g. or 49·3% [$Zn(NO_3)_2.2N_2O_4$ requires N_2O_4, 49·3%].

Products of Reaction with Ethyl Ether.—The evolved gases were passed through a guard tube containing calcium chloride, and absorbed in an ice-cold, very dilute solution of sodium hydroxide. The acetaldehyde was redistilled from the alkaline solution into an aqueous-alcoholic solution of dimedone, and characterised as the dimedone derivative. The presence of acetaldehyde was confirmed by passing the gases evolved from the reaction mixture directly into an acid solution of 2 : 4-dinitrophenylhydrazine. The anhydrous calcium nitrate used in comparison experiments was obtained by heating the tetrahydrate (prepared from A.R. calcium carbonate) at 160°. Its purity was confirmed by determining the extinction coefficient of a standard solution, at 3020 A., by means of an ultra-violet spectrophotometer.

Decomposition of Zinc Nitrate.—The tube containing the zinc nitrate was immersed in a fused sodium nitrate–potassium nitrate bath controlled at the desired temperature. A stream of dry oxygen was passed over the zinc nitrate, and the gas stream (containing oxides of nitrogen produced by decomposition) was passed through an absorption trap containing standard sodium hydroxide solution. The absorption trap was replaced at frequent intervals, and the remaining alkali titrated against standard acid.

The authors are indebted to the Department of Scientific and Industrial Research for a Maintenance Grant to one of them (J. L.).

THE UNIVERSITY, NOTTINGHAM. [*Received, March 19th*, 1951.]

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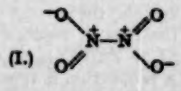
629. *The Liquid Dinitrogen Tetroxide Solvent System. Part VIII.* Rates, and Possible Mechanisms, of Reaction of Zinc with Liquid Dinitrogen Tetroxide.*

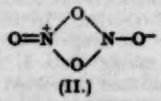
By C. C. ADDISON and J. LEWIS.

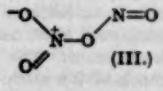
Experimental conditions are described under which the measured rate of reaction between dinitrogen tetroxide and zinc metal is considered to be uninfluenced by diffusion, passivity, or products of reaction, and thus to represent the true rate of chemical reaction. Under these conditions, reaction rates have been determined over the available liquid temperature range (−11·2° to 21·3°). These rates are considered in the light of the possible active species. Two mechanisms of reaction appear to operate. Below 14° the predominant reaction is attibuted to the $[NO^+][NO_3^-]$ ion-pairs ($E_A = 4500$ cals.); above 14° the reaction ($E_A = 26{,}000$ cals.) is considered to involve the fission of the N–N bond at the zinc surface, followed by reaction between zinc and nitrogen dioxide to give zinc oxide. This rate-determining step is followed by further reaction of the zinc oxide to give the compound $Zn(NO_3)_2.2N_2O_4$.

LIQUID dinitrogen tetroxide is known to contain a small quantity of nitrogen dioxide, the concentration depending on the temperature. In order to account for the difference between molar polarisation and molar refraction in the liquid, the presence of $[NO^+][NO_3^-]$ ion-pairs has been postulated in Part IV (*J.*, 1951, 1294). Alternatively, this difference could be attributed to $[NO_3^+][NO_3^-]$ ion-pairs. In addition to the undissociated molecules, the liquid therefore contains, or can give rise to, a number of species, some or all of which may take part in the reactions between liquid dinitrogen tetroxide and metals. In consequence, a large number of mechanisms is theoretically possible.

The study of reaction mechanism gains further significance from the fact that the structure of the dinitrogen tetroxide molecule has now been shown by Broadley and Robertson (*Nature*, 1949, **164**, 915) to be (I) in the solid state. It is to be presumed that this structure is predominant


(I.)


(II.)


(III.)

in the liquid state also, yet it is this particular structure which is least readily reconciled with the ionic reactions of liquid dinitrogen tetroxide. Direct reaction between zinc metal and the

* Part VII, preceding paper.

tetroxide molecule (I) to give zinc nitrate and nitric oxide involves an unlikely atom transfer across the weak N–N bond, whereas either of the structures (II) (Longuet-Higgins, *Nature*, 1944, **153**, 408) or (III) (Pauling, "The Nature of the Chemical Bond," Cornell Univ. Press, 1945, p. 271) would require electron transfer only in these reactions.

The present paper is concerned with the deductions regarding mechanism which can be made from a study of the influence of temperature on reaction rates; consistently with the above, the experiments suggest that the undissociated molecule does not, in fact, take part directly in reaction with metals in such a way as to involve atom transfer.

Experimental.—Zinc blocks. Zinc metal (A.R.; arsenic free) was cast into rectangular blocks measuring approximately 0·6 × 0·6 × 2 cm., weight 5 g., surface area 5 cm.². The surfaces of the block were smooth, and the surface area could therefore be determined with accuracy by micrometer measurement of the block dimensions.

Reaction tube. A hole, approx. 2 mm. in diameter, was bored through the zinc block, and the block, held on a glass hook formed on the end of a glass rod, was suspended in 15 ml. of liquid dinitrogen tetroxide [prepared as described in Part II (*J.*, 1949, S 218)] contained in a 12 × 2·5 cm. Pyrex-glass tube. The tube was fitted with side arm (for venting) guarded by phosphoric oxide; the glass rod carrying the zinc block was attached tightly into a Quickfit Type ST 4/2 stirrer gland, which fitted the B.24 ground joint on the reaction tube. The small area of stirrer-gland metal which was exposed to the tetroxide vapour inside the reaction tube was prevented from contaminating the tetroxide by a thin coating of silicone grease. The stirrer gland was connected to an electric motor, which was so geared that the zinc block could be rotated at speeds up to about 300 r.p.m. The reaction tube was immersed, to within 2 cm. of its top, in a thermostat.

Results and Discussion.

Preliminary Study of Conditions influencing Reaction Rates.—(a) *Condition of surface.* The method used to prepare the metal surface for reaction with the tetroxide has a considerable influence on reaction rates; typical observations are collected in Table I, and throughout the experiments discussed below the zinc surface was prepared for reaction by method (4), Table I.

Table I.

Treatment of surface.	Rate of loss of zinc (unstirred) (g. × 10^{-4}/cm.²).		
(1) Exposed to atmosphere for long period or heated for short period (*e.g.*, at 150° for 20 mins.)	Scarcely detectable		
(2) Acid-washed; zinc immersed in 2N-HCl for 10 mins., washed with water, alcohol, ether, and dried in vacuum desiccator	5·3 (10 mins. at 18°)	3·2 (1 hour at −11°)	7·8 (1 hour at 15°)
(3) Alkali-washed; as for (2) but 2N-HCl replaced by 5N-NaOH	7·1 (10 mins. at 18°)	4·2 (1 hour at −11°)	13·8 (1 hour at 15°)
(4) Surface freshly filed, washed with water, alcohol, ether, dried in vacuum desiccator	Results similar to (3) above		

(b) *Rate of stirring.* The measured rates of a heterogeneous reaction involving solid–liquid interfaces may (i) represent the true reaction rate, or (ii) reflect (in systems inadequately stirred) the rate of diffusion of reaction products from the surface. The rates of reaction of zinc have therefore been determined over a range of stirring rates, and the results are shown in curve *A* (Fig. 1). Each experimental point represents the quantity of zinc lost from 1 cm.² of surface on immersion in dinitrogen tetroxide at 17° for 15 minutes. Above a stirring rate of about 40 r.p.m., the rate of loss of zinc remained constant at rates up to 300 r.p.m. This is considered to indicate that at stirring rates greater than 40 r.p.m. the measured rate is a true rate of chemical reaction and is not influenced by any diffusion process. All reaction rates discussed below were measured with stirring rates of 250 r.p.m.

(c) *Influence of reaction products.* In most heterogeneous reactions cited in the literature, the products of reaction have no further chemical action in the system; their only effect is to hinder physically the initial reaction, and therefore to reduce the reaction rate. In consequence, stirring results in an increase in rate of reaction. In the present system, the reverse is the case; as the stirring rate is increased over the range 0—40 r.p.m., the rate of reaction shows an appreciable decrease. The reaction taking place is $Zn + 4N_2O_4 = Zn(NO_3)_2.2N_2O_4 + 2NO$. Although much of the nitric oxide produced is evolved as such, a proportion is retained in the liquid as dinitrogen trioxide. A separate investigation (Part IX, following paper) has shown that dinitrogen trioxide, in solution in the tetroxide, reacts with zinc at a greater rate than does the liquid tetroxide alone. The higher rate of reaction in the unstirrred system (Fig. 1, curve *A*) is therefore attributed to the accumulation of the more active trioxide in the immediate

neighbourhood of the surface. Stirring leads to the dispersion of this accumulated trioxide throughout the bulk of the tetroxide, and consequently results in a decrease in the rate of reaction. The rate of reaction represented by the level portion of curve *A* may be regarded as typical of dinitrogen tetroxide alone, since the concentration of the trioxide, when dispersed throughout the volume of tetroxide used, has been shown to be insignificant over the time ranges employed. For example, the highest reaction rates (Fig. 2, curve *B*) are equivalent to the production of 0·01 g.-mol./l. of trioxide, all the nitric oxide produced being assumed to be converted into trioxide. This concentration is without detectable influence on reaction rates (Part IX, following paper). In this connection it is of interest that if solutions are used in which the concentration of dinitrogen trioxide produced is sufficiently high to influence the reaction rate, this rate may be appreciably decreased by bubbling a gentle stream of oxygen over the surface of the metal.

In many solid–liquid reactions in which diffusion is considered to influence the reaction rate (*e.g.*, King and Braverman, *J. Amer. Chem. Soc.*, 1932, **54**, 1744; Bircumshaw and Riddiford, *J.*, 1951, 598), the products of reaction are soluble in the liquid phase, and the rate of reaction is influenced by the rate at which molecules of the active species can diffuse through that region, in immediate contact with the surface, containing a high concentration of dissolved reaction

FIG. 1.

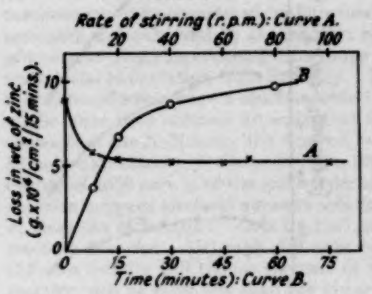
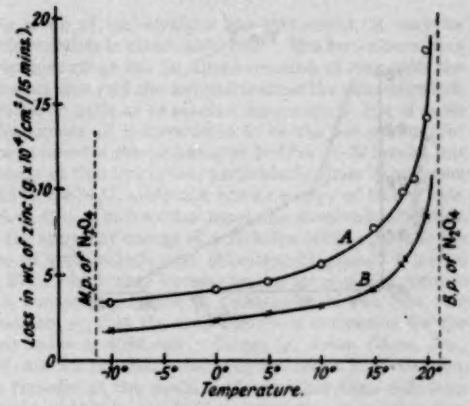


FIG. 2.



product. Again, the active species (*e.g.*, acid or iodine) is chemically independent of (and is not formed by dissociation of) the aqueous medium. In the zinc–dinitrogen tetroxide reaction different conditions are involved. There is no concentration gradient in the neighbourhood of the surface, since the reaction product $Zn(NO_3)_2.2N_2O_4$ is insoluble in the tetroxide, and the dinitrogen trioxide is readily dispersed by stirring; the active species may be either the tetroxide molecules themselves or the dissociation products with which they are in equilibrium. Therefore provided that the liquid medium has unhindered access to the surface, there is no diffusion mechanism which can operate. With certain metals (*e.g.*, sodium) the rate of reaction falls rapidly with time of contact, ultimately reaching negligible proportions. This may be attributed directly to the cohesive nature of the film of sodium nitrate produced in the reaction. In the case of zinc, however, the reaction product is readily detached from the surface; the rate of reaction is constant, under standard conditions, during the first 15 minutes, and the reaction will continue indefinitely. Experimental observations therefore indicate that the liquid has unhindered access to the surface, and in consequence the diffusion processes which must be considered in many heterogeneous reactions have no application in the present system.

(d) *Period of immersion.* Curve *B* (Fig. 1) shows the change in the rate of reaction of zinc for various periods of immersion. The experimental points shown were obtained at 18·5°, and a stirring rate of 250 r.p.m. During the first 15 minutes there is a linear relation between the amount of zinc reacting and the time of immersion. Thereafter the rate of attack diminishes; this is attributed to the development of passivity by the zinc. Periods of 15 minutes' immersion have been employed throughout in the determination of temperature coefficients; the loss in

weight of the zinc (and the accuracy of measurement) is thus the maximum available experimentally if interference from passivity effects is to be avoided.

Influence of Temperature on Rate of Reaction.—The experiments described above show that the optimum conditions for the determination of true rates of reaction in this system involve (1) a high stirring rate (250 r.p.m.), (2) a short period of immersion (15 minutes), (3) a volume of tetroxide sufficiently large that the concentration of trioxide produced is negligible (15 ml.), and (4) a freshly filed surface. Under these experimental conditions, the variation of reaction rate with temperature has been studied, and the results are shown in curve *B* (Fig. 2). Over the major portion of the temperature range the temperature coefficient is small, but increases rapidly near the b. p. of the liquid. It is of interest that, although variations in experimental conditions influence the magnitude (and the accuracy of determination) of the reaction rate, the general form of the curve is maintained. For example, the experimental points shown on curve *A* were obtained without stirring, zinc being used which had been given a preliminary acid wash, and the loss in weight of the zinc block was determined during one hour's immersion. Although these conditions vary widely from the ideal conditions, the general shape of curve *A* closely resembles that of *B*.

FIG. 3.

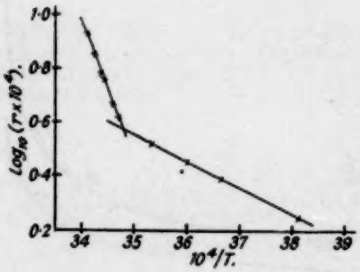


FIG. 4.

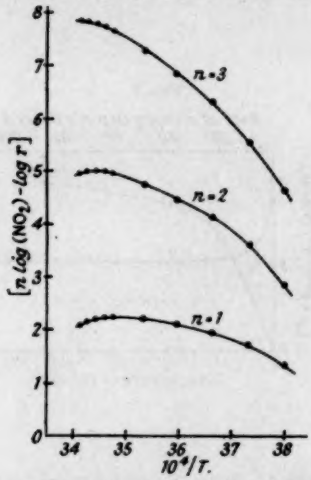


Fig. 3 shows the relation between $\log_{10} r$ [where r is the rate of reaction of zinc (g./15 mins.) per cm.^{2}] and the inverse of the absolute temperature. If it is assumed, as a first step, that r is proportional to the velocity constant k, then since $k = Be^{-E/RT}$, it appears from Fig. 3 that two distinct mechanisms of reaction are operating within the liquid temperature range. The true relationship between the rate of reaction and k is given by an equation of the form :

$$\text{Rate of reaction} = k\,[\text{Zn}][\text{X}]^n$$

where X represents the active species. If the zinc loss is expressed per unit area, then the term [Zn] may be eliminated and therefore

$$\log r = -E/RT + n \log [\text{X}] + A \qquad . \; . \; . \; . \; . \; . \; . \; (1)$$

where A is a constant.

The points recorded in Fig. 3 appear to lie on two straight lines; this would imply that the concentration of the active species remains virtually constant over the temperature range, *i.e.*, for both mechanisms. However, it is not possible to dismiss, without further consideration, the possibility that the points should be regarded as falling on a continuous curve. It is clear from Fig. 3 and equation (1) that such a continuous curve could only arise if the concentration of the active species varies considerably with temperature. Of the available species, the concentration of the N_2O_4 molecules may be regarded as constant, since the degree of dissociation into NO_2 molecules is very small in the liquid phase (Sone, *Tohoku Imp. Univ. Sci. Rep.*, 1922, 11, 139) and the concentration of ion-pairs (Part IV, *loc. cit.*) is negligible with respect to the

tetroxide present. The concentration of ion-pairs is a function of the absolute temperature only (Part IV), and is thus not sufficiently variable to produce the observed effects over the full range of temperature. Molecules of NO_2 form the only species present whose concentration does vary considerably with temperature, and the experimental results have therefore been considered from the point of view that NO_2 may be the active species. Fig. 4 shows the relation between $[n \log [NO_2] - \log r]$ and $1/T$ for possible values of n (*i.e.*, 1, 2, and 3). The concentration values for nitrogen dioxide were interpolated, where necessary, from the values given by Sone (*loc. cit.*), which are as follows:

Temperature	−16°	0°	7·2°	11·2°	20°
Nitrogen dioxide, %	0·0	0·15	0·29	0·37	0·72

If an NO_2 mechanism operates, then the points shown in Fig. 4 for one of the values of n should lie on a straight line, with a positive slope. This condition is not fulfilled, and it is deduced that the free NO_2 molecules take no part in the reaction between zinc and liquid dinitrogen tetroxide. This conclusion is without prejudice to the mechanism postulated below, which involves only those NO_2 molecules produced by fission of N_2O_4 molecules of higher activation energy at the zinc surface.

In consequence of the above, the results shown in Fig. 3 are regarded as falling on two straight lines; two distinct mechanisms therefore operate, with a demarcation temperature of 14°.

Low-temperature Mechanism.—From the slope of the straight line concerned, it may be calculated that the activation energy for this reaction is about 4500 cals. The two alternative mechanisms to be considered for this temperature range are (*a*) direct reaction of zinc with the tetroxide molecule, and (*b*) the reaction between zinc and the ion-pairs, since the concentration of ion-pairs over this concentration range varies so little as to involve the results in Fig. 3 in an inappreciable deviation from linearity. Mechanism (*a*) is considered to be the less attractive; it is difficult to envisage a reaction which must involve the breaking of N–O or N–N bonds, but at the same time involves an activation energy of this low order, particularly since it has been shown that the N–N bond, the weakest bond in the N_2O_4 molecule, has an energy of 12,800 cals. (Giauque and Kemp, *J. Chem. Physics*, 1938, **6**, 40). On the other hand, the observed activation energy of 4500 cals. is of the same order as the apparent energy of activation (4230 cals.) for the reaction between zinc and aqueous solutions of hydrochloric acid (Moelwyn-Hughes, "Kinetics of Reaction in Solution," O.U.P., 1947, p. 372), which may be assumed to involve zinc–proton electron transfer. Although diffusion is a controlling factor in this zinc–acid reaction, the diffusion barrier will reduce the rate of reaction, so that the true energy of activation for the reaction will be even less than the apparent value of 4230 cals. James (*J. Amer. Chem. Soc.*, 1943, **65**, 39) obtained the value $E_A = 5000$ cals. for the magnesium–hydrochloric acid reaction, where the rate-controlling step is electron transfer at the metal surface rather than diffusion.

It is therefore considered that the most probable mechanism operative over the low-temperature range involves an electron-transfer reaction between the zinc metal and the ion-pairs. These ion-pairs may be of the form $[NO^+][NO_3^-]$ or $[NO_2^+][NO_3^-]$. On the latter alternative, reaction with metals should produce a metal nitrite as a final, or at least an intermediate, product of reaction. It is significant that no metal–dinitrogen tetroxide reactions yet studied have given even a trace of nitrite in the product. Nitrite is also an improbable intermediate, since sodium nitrite has been found to be entirely unchanged after several weeks in contact with liquid dinitrogen tetroxide. Although a direct analogy between sodium and zinc nitrite may not be fully justified (and anhydrous zinc nitrite is unknown in the solid state), the available chemical evidence does not support a structure $[NO_2^+][NO_3^-]$ for the ion-pairs, and the low-temperature mechanism is therefore considered to be $Zn + 2[NO^+][NO_3^-] = Zn[NO_3]_2 + 2NO$.

High-temperature Mechanism.—From the slope of the straight line concerned, the energy of activation is approximately 26 kcals. This is higher than the activation energy normally associated with simple electron-transfer processes. Since the active species is again independent of temperature, the reaction at higher temperatures appears to arise primarily from the dinitrogen tetroxide molecules themselves. The reaction results in the formation of nitrate, and must therefore involve the breaking of more than one of the bonds concerned. A value of $E_A = 26$ kcals. is consistent with such a process; Giauque and Kemp (*loc. cit.*) have shown that for the reaction

$$N_2O_4 = 2NO_2, \qquad \Delta H = 12{,}873 \text{ cals.}$$

and for

$$NO_2 = NO + \tfrac{1}{2}O_2, \qquad \Delta H = 13{,}562 \text{ cals.}$$

It is considered improbable that the reaction occurs in a single stage, since the nature of the products involves the fission of more than one bond in the N_2O_4 molecule. Structure (I) being assumed for the tetroxide molecule, the first bond to be broken (presumably the weaker N–N bond) would again lead to the unlikely formation of nitrite as product if a single-stage $Zn + N_2O_4 \longrightarrow Zn(NO_2)_2$ operated.

Present experimental evidence is in agreement with the following postulated mechanism: (1) The impact of the N_2O_4 molecules at the metal surface results in the fission of the N–N bond to give two NO_2 units. (2) For those N_2O_4 molecules possessing the requisite initial energy, the NO_2 units produced are sufficiently activated to react with the metal as follows: $Zn + NO_2 = ZnO + NO$. (3) The zinc oxide reacts with dinitrogen tetroxide as follows: $ZnO + 4N_2O_4 = Zn(NO_3)_2,2N_2O_4 + N_2O_3$.

Reaction (3) is known to proceed readily, and stages (1) and (2) above are considered to be the rate-determining steps.

The available temperature range over which dinitrogen tetroxide is in the liquid state necessarily restricts any kinetic studies to a narrower temperature range than would otherwise be desirable. However, the mechanisms postulated above are in accord with all experimental evidence now available, and form the theoretical basis on which reactions with other metals will be studied.

THE UNIVERSITY, NOTTINGHAM. [*Received, March 19th, 1951.*]

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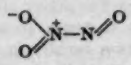
630. *The Liquid Dinitrogen Tetroxide Solvent System. Part IX.* Products, Rates, and Possible Mechanisms of the Reaction of Zinc with Liquid Dinitrogen Trioxide–Tetroxide Mixtures.*

By C. C. ADDISON, J. LEWIS, and R. THOMPSON.

The rate of reaction between zinc metal and liquid dinitrogen tetroxide is increased by addition of dinitrogen trioxide. Rates of reaction between zinc and dinitrogen trioxide–tetroxide mixtures over the 0—40% trioxide concentration range, and the electrical conductivity of the mixtures over the 0—70% range, have been measured. Notwithstanding the higher reaction rate, the product of reaction with the trioxide–tetroxide mixtures is identical with the compound $Zn(NO_3)_2,2N_2O_4$ produced by reaction of zinc with pure dinitrogen tetroxide. Possible mechanisms of reaction of the trioxide with zinc are considered; the experimental results are satisfactorily explained on the assumption that no species peculiar to dinitrogen trioxide take part in the reaction, but that the trioxide augments mechanisms already in operation between zinc and dinitrogen tetroxide (Part VIII, preceding paper).

THE experiments now described were carried out in consequence of the observation that the rate of reaction between zinc metal and dinitrogen trioxide–tetroxide mixtures was much greater than that with the tetroxide alone. It was already known that reaction between zinc and nitrosyl chloride (in solution in the tetroxide) is rapid (Part I, *J.*, 1949, S 211), and the high rate of reaction with dinitrogen trioxide appeared to be capable of interpretation on the basis that this molecule could be regarded as a nitrosyl compound. If such was the case, then dinitrogen trioxide would become a formal " acid " in this solvent system, and would react as nitrosyl nitrite. This behaviour would be consistent with either of the structures postulated for the trioxide molecule, *i.e.*, (I) and (II), except that the formation of nitrosyl nitrite involves

(I.)  O=N–O–N=O (II.)

the fission of an N–N bond in structure (I), but an N–O bond in structure (II). Structure (II) is proposed by Liefer (*J. Chem. Physics*, 1940, **8**, 301) on the basis of the ready exchange of the ^{15}N isotope between NO and NO_2 molecules, and is favoured by Sidgwick (" Chemical Elements

* Part VIII, preceding paper.

and their Compounds," O.U.P., 1950, Vol. 1, p. 688). Although this stucture may represent that of the intermediate compound formed during isotope exchange between NO and NO_2 molecules in the gaseous state, it is considered that the structure of the dinitrogen trioxide molecule in the liquid state is better represented by (I), both by analogy with the tetroxide, and on the basis of Ingold's evidence for this structure (*Nature*, 1947, **159**, 743). Structure (I) is therefore assumed in the considerations below.

There are at least two objections to the formulation of dinitrogen trioxide as nitrosyl nitrite. First, the formal acid–metal equation $Zn + 2[NO^+][NO_2^-] = Zn(NO_3)_2 + 2NO$ would require the formation of nitrite. Analysis of the product has shown that this is not the case. Secondly, Le Fèvre (*Nature*, 1932, **130**, 400) states that the tautomeric electron-attraction of the nitroso-group is greater than that of the nitro-group; fission of the N–N bond would therefore lead to $[NO_2^+][NO^-]$ rather than $[NO^+][NO_2^-]$.

The experiments described below have therefore been carried out in order to assess the rôle which dinitrogen trioxide may be regarded as playing in the dinitrogen tetroxide solvent system, and to determine how far the nature of the reaction can be reconciled with the mechanism postulated in Part VIII for reaction between zinc and the pure tetroxide.

Results and Discussion.

The identity of the product of reaction between zinc and liquid dinitrogen trioxide–tetroxide mixtures was established by two methods.

(a) *Ignition.* By ignition of a known weight of the powder to zinc oxide, the zinc content was shown to be 17·5%. On initial heating, the compound evolved dinitrogen tetroxide only; evolution of tetroxide ceased at about 120° and the remaining white powder (zinc content, 34·6%) was shown to be pure zinc nitrate. The ignition experiment therefore indicated that the product of reaction was the compound $Zn(NO_3)_2,2N_2O_4$.

(b) *Hydrolysis.* Since the present experiments were particularly concerned with the detection of nitrite, or combined dinitrogen trioxide, in the reaction product, the ignition method of analysis is less desirable because of the small variation in zinc content over the range of possible products. On the other hand, the quantity of nitrite produced on hydrolysis of the compound enables a definite conclusion to be reached. This is illustrated in the table below. On hydrolysis of the product in 0·1N-sodium hydroxide solution, two equivalents of nitrite were produced. This confirms that the product of reaction is $Zn(NO_3)_2,2N_2O_4$, uncontaminated by any other of the possible products.

Possible products	Equivs. of nitrite produced on hydrolysis	Zinc content, %
$Zn(NO_3)_2,2N_2O_4$	2	17·51
$Zn(NO_3)_2,N_2O_3,N_2O_4$	3	18·29
$Zn(NO_3)_2,2N_2O_3$	4	19·15
$Zn(NO_3)_2,2N_2O_4$		
$Zn(NO_3)_2,N_2O_3,N_2O_4$	5	20·09
$Zn(NO_3)_2,2N_2O_3$	6	21·13

The product of reaction between zinc and mixtures containing up to 70% of dinitrogen trioxide is therefore identical with that produced from zinc and pure dinitrogen tetroxide. Similarly, it has been shown that the reaction between metallic sodium and dinitrogen trioxide–tetroxide mixtures produces sodium nitrate free from any trace of nitrite. These results indicate that the mechanism of reaction between these metals and dinitrogen trioxide must be closely interlinked with that involving the tetroxide.

Rates of Reaction.—The influence of dinitrogen trioxide concentration on the rate of reaction with zinc is shown in Fig. 1 (curve *A*). The measurements recorded were obtained for 15-minute immersion periods at 0°, a stirring rate of 250 r.p.m. being used. Preliminary experiments on which the choice of these experimental conditions was based (including a study of the stability of tetroxide–trioxide mixtures) are described on p. 2842. The results shown in Fig. 1 cover a concentration range of about 0—40% of trioxide; the increase in reaction rate in the presence of trioxide is pronounced, the rate in a mixture containing 40% of trioxide being eight times that in the pure tetroxide. It is of interest that the rate of reaction appears to be a linear function of the square root of the dinitrogen trioxide concentration (Fig. 1, line B). For experimental reasons a kinetic study of the present system, similar to that described in Part VIII (*loc. cit.*) for the zinc–dinitrogen tetroxide reaction, presents considerable difficulties. Although it is observed that for solutions of any given concentration the rate of reaction increases with increase in temperature, the stability of the trioxide–tetroxide mixtures (especially at temperatures above 0°) is such that it was not found possible to maintain the concentration of

the mixture at a sufficiently constant value over the full range of temperature to permit the accurate determination of activation energies for this reaction.

Electrical Conductivity of Mixtures.—The addition of dinitrogen trioxide to the tetroxide increases the electrical conductivity. Conductivity measurements over a wide range of concentration are given below. As with dinitrogen tetroxide alone (Part III, *J.*, 1951, 1289)

N_2O_3 concn., % (wt./wt.)	0	8·8	28·0	31·5	34·8	40·5	43·0	55·5	61·5	73·0
κ, ohm^{-1} cm.$^{-1}$ at −10°	6 $\times 10^{-13}$	1·7 $\times 10^{-10}$	6·7 $\times 10^{-9}$	7·5 $\times 10^{-8}$	8·9 $\times 10^{-8}$	1·2 $\times 10^{-7}$	1·3 $\times 10^{-7}$	2·5 $\times 10^{-7}$	4·9 $\times 10^{-7}$	1·3 $\times 10^{-6}$

the trioxide–tetroxide mixtures show a positive temperature coefficient of conductivity. From the results recorded in the third table, the temperature coefficient has a mean value of $0{\cdot}03 \times 10^{-7}$ ohm^{-1} cm.$^{-1}$ per degree.

N_2O_3 concn., %	Temp.	$10^7\kappa$, ohm^{-1} cm.$^{-1}$	N_2O_3 concn., %	Temp.	$10^7\kappa$, ohm^{-1} cm.$^{-1}$
58·0	−13°	3·6	61·5	−10°	4·9
	−24	3·4		−14	4·5
	−36	3·1		−40	3·8
	−40	3·0			

Possible Mechanisms of Reaction.—The fact that the product of reaction with trioxide–tetroxide mixtures, at any concentration, is identical with that formed with the tetroxide alone

FIG. 1.

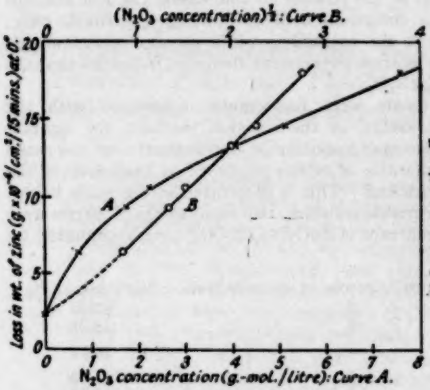
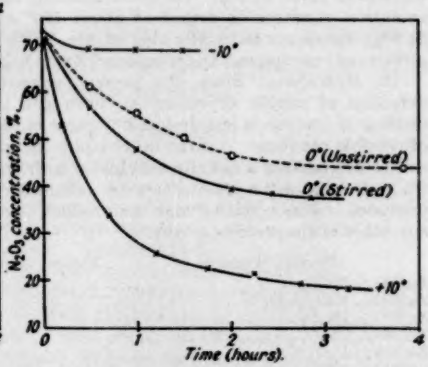


FIG. 2.



is regarded as strong evidence that the mechanism of the more rapid reactions with the mixture does not involve any species peculiar to the trioxide molecule. Thus, reaction of the trioxide as nitrosyl nitrite would involve the formation of nitrite as the final, or at least an intermediate, product. No nitrite occurs in the final product. Sodium metal reacts with trioxide–tetroxide mixtures to give sodium nitrate, and since sodium nitrite is quite stable in trioxide–tetroxide mixtures it may be presumed that the formation of nitrite as an intermediate in the zinc reaction is also improbable.

However, the experimental observations given above are readily interpreted on the basis that dinitrogen trioxide can augment reaction mechanisms which are already in operation between zinc and dinitrogen tetroxide (Part VIII, preceding paper).

Dinitrogen trioxide is considered to be capable of increasing the velocity of the reactions occurring by either mechanism. Since both mechanisms may well operate under appropriate conditions, it is not necessary, or desirable, to place emphasis on either mechanism. The reaction in pure liquid dinitrogen tetroxide at low temperatures necessarily involves ion-pairs only, and not free ions, since the low dielectric constant of the pure tetroxide (2·42; Part IV, *J.*, 1951, 1294) prevents separation into discrete ions. Again, the low dielectric constant is a direct consequence of the symmetry, and hence the lack of dipolar character, in the N_2O_4 molecule. However, the N_2O_3 molecule [assumed to have structure (I)] does not possess this symmetry. It is therefore to be expected that the molecule will show dipolar properties, and its addition to liquid dinitrogen tetroxide should result in an increase in the dielectric

constant of the medium. In consequence, some dissociation of the ion pairs may be considered to occur; this is in accord with the increase in the electrical conductivity of the liquid, and the well-known stability of the NO^+ and NO_3^- ions is consistent with the observed positive temperature coefficient of conductivity. We may assume that reaction between metal atoms and free ions is a process which occurs somewhat more readily than that between the metal and the ion pairs, and it follows from the relation $k = Pe^{-E/RT}$ that a small decrease in the energy of activation E can give rise to a relatively large increase in the velocity constant k. However, the small concentration of ion-pairs which is considered to exist in the pure tetroxide limits the significance to be attached to this particular aspect. A more significant factor is the increase in the ionic concentration which may result from the relative instability of the dinitrogen trioxide molecule. The complete equilibrium between the species present in the tetroxide may be represented as follows:

$$N_2O_4 \underset{(1)}{\rightleftharpoons} 2NO_2 \underset{(2)}{\rightleftharpoons} [NO^+][NO_3^-] \underset{(3)}{\rightleftharpoons} NO^+ + NO_3^-$$

Increase in the dielectric constant of the medium will result in displacement of equilibrium (3). There is considerable chemical and physical evidence to suggest that the N–N bond in the trioxide molecule is much weaker than in the tetroxide; the molecule does not exist in the gaseous state, and in the liquid state the equilibrium $N_2O_3 \rightleftharpoons NO + NO_2$ is no doubt displaced further towards the right-hand side than in the case of the tetroxide equilibrium (1) above. As a result, the addition of dinitrogen trioxide to the tetroxide will give rise to a higher proportion of NO_2 molecules in the medium, and in consequence a greater concentration of NO^+ and NO_3^- ions. This may be compared with the reverse reaction which can be observed in solutions of dinitrogen tetroxide in pure nitric acid. Goulden (Ph.D. Thesis, London, 1949) found that addition of potassium nitrate to such solutions resulted in an increase of yellow colour in the solution. This coloration was attributed to the presence of nitrogen dioxide, and the increase in colour to a shift in the equilibrium $NO^+ + NO_3^- \rightleftharpoons 2NO_2$ towards the right-hand side on addition of potassium nitrate.

Further evidence for this mode of action of the trioxide is provided by the linear relation between the rate of reaction and the square root of the trioxide concentration. Direct participation by the trioxide in the reaction might have been expected to involve a relation between reaction rate and some power (1, 2, or 3) of the trioxide concentration (as occurs in the nitrosyl chloride reaction described in the following paper). A square-root relationship is unusual, and is more readily explained on the assumption that it is this power of the concentration which is related to (say) the concentration of ions in the medium.

At the higher temperatures we may regard the reaction between a dinitrogen trioxide molecule and a zinc atom as involving the fission of the N–N bond, followed by reaction between zinc and the nitrogen dioxide so produced. This second stage is identical with that considered to occur with the tetroxide, but since the N–N bond in the trioxide is weak, then the sum of the energies required to break first the N–N bond in the trioxide molecule, and secondly the N–O bond in the NO_2 molecule produced, will be less than the corresponding total energy for the tetroxide molecule. In consequence, the energy of activation for the Zn–N_2O_3 reaction will be less than that for the Zn–N_2O_4 reaction, which leads directly to an increase in the rate of reaction. Such a mechanism results in the formation of the same final product as in the case of the tetroxide.

In view of the above, it is clearly unnecessary to seek a mechanism which is peculiar to the trioxide (in addition to those believed to occur in the pure tetroxide) in order to explain the identity of the reaction products or the higher rates of reaction.

Experimental.

Preparation of Dinitrogen Trioxide–tetroxide Mixtures.—When nitric oxide was bubbled through liquid dinitrogen tetroxide at −5° the rate of absorption was slow; when using about 10 ml. of the liquid tetroxide at this temperature, it was necessary to bubble the nitric oxide for several hours to prepare a mixture containing 5—10% of dinitrogen trioxide. Although it is probable that the absorption of nitric oxide is greater at lower temperatures, the lower limit of temperature is set by the freezing point of the tetroxide (−11·2°). A sufficient concentration range was not therefore readily available by this method. Methods of preparation involving nitric acid (or dilute sulphuric acid) were undesirable in the present work because of the moisture carried with the evolved gases, and the consequent difficulty in eliminating moisture from the liquid product. The mixtures used in the reactions with metals and in conductivity measurements were therefore prepared from concentrated sulphuric acid and solid sodium nitrite as follows. About 250 g. of sodium nitrite were contained in a 500-ml. flask fitted with a dropping funnel containing concentrated sulphuric acid. The acid was added to the nitrite at the rate of approx. 1 ml. per minute, and the evolved mixture of nitric oxide and dinitrogen tetroxide gases was passed

through a series of drying tubes (equivalent to a tube 1·5 m. long and 2 cm. in diameter) packed with asbestos wool and phosphoric oxide. The dry gas mixture was passed into a condenser similar to that shown in Fig. 1(a) of Part II (*J.*, 1949, S 218), kept at −40° in a solid carbon dioxide–alcohol bath, an ink-blue condensate being obtained. Under these conditions the liquid product contained about 75% of dinitrogen trioxide, and was prepared at the rate of about 15 ml. per hour. More dilute solutions of the trioxide were obtained when required by dilution of the above mixture with pure tetroxide.

Analysis of Mixtures.—Because of the unstable nature of dinitrogen trioxide–tetroxide mixtures, it was essential to use a method of analysis sufficiently rapid to be completed within a few minutes of the time when the mixture was being used. In the reactions with metals and in conductivity measurements it was also desirable to analyse the mixture before, and immediately after, the experiment in order to confirm that no appreciable decomposition had taken place. Withdrawal of samples of the mixtures for chemical analysis involved considerable practical difficulties, and the volatility of the liquid gives rise to appreciable experimental errors in such a technique. For present purposes the composition of the mixture was available with sufficient accuracy from its m. p., which was determined from warming curves as described in Part II (*loc. cit.*). The liquidus curve given by Baum and Roberts (*Compt. rend.*, 1919, **169**, 968) was used. These authors quote a value of −11·5° for the f. p. of pure liquid dinitrogen tetroxide. Wittorf (*Z. anorg. Chem.*, 1904, **41**, 85) records this freezing point as −10·0°. However, when corrections are made for these deviations from the true value (−11·2°), the two liquidus curves for trioxide–tetroxide mixtures are in close agreement.

The thermometers used were calibrated by using a series of standard liquids, *viz.*, water, liquid dinitrogen tetroxide, carbon tetrachloride, mercury, chlorobenzene, and chloroform. The error in f. p. determinations did not exceed 0·2°, which is equivalent to a maximum error in the trioxide concentration of 0·1—0·4%, depending on the slope of the liquidus curve over the concentration range.

Stability of Mixtures.—In order to determine appropriate experimental conditions under which the dinitrogen trioxide–tetroxide mixtures would be stable during the 15-minute immersion periods employed for the measurement of reaction rates, the stability of these mixtures has been determined over a range of temperature and concentration. The full curves in Fig. 2 show the rate of decrease in trioxide concentration at three temperatures. In each case the same original mixture containing 73% of trioxide (prepared as above) was used. 20 Ml. of the mixture were contained in a reaction tube similar to that described in Part VIII (*loc. cit.*) and was stirred at a rate of 250 r.p.m., the stirrer being a glass stirrup similar in dimensions to the zinc block used in the measurement of reaction rates. At −10°, solutions containing up to about 70% of trioxide were stable for long periods, the trioxide concentration varying by not more than 0·05% in 15 minutes. At 0°, solutions containing more than 40% of trioxide changed rapidly in concentration. In the 0—40% concentration range, the trioxide concentration changed at rates up to 0·5% in 15 minutes; 0° was a convenient temperature at which to determine the rates of reaction with zinc, and therefore the results recorded in Fig. 1 were obtained at this temperature and were restricted to the 0—40% concentration range. At +10°, solutions containing more than 20% of trioxide were unstable.

The broken curve shows the rate of decrease in trioxide concentration at 0° in the absence of stirring. Comparison with the corresponding rates for stirred solutions shows that stirring has not a considerable effect on the rate of decomposition, and reduces the trioxide concentration at which mixtures may be regarded as stable at this temperature by only about 5%.

Period of Immersion.—The influence of time of immersion is shown below. There is a linear relation between the loss in weight of zinc and the period of immersion, so that for periods up to 15 minutes the rates recorded in this table (and in Fig. 1) are regarded as true rates of reaction. The rates of reaction were measured precisely as described in Part VIII (*loc. cit.*); stirring rates of 250 r.p.m. were employed throughout, since under these conditions the rate of reaction was independent of stirring rate.

(N_2O_4 concentration, 39·0%.)

Period of immersion at 0° (mins.)	7	10	15
Loss in weight of zinc (g. × 10^{-4}/cm.^{2})	8·5	12·1	18·1

Density of Mixtures.—In calculating the concentration of dinitrogen trioxide in the mixture in g.-mol./l. units, the values for the density of the trioxide given by Geuther (*Annalen*, 1888, **245**, 96) were used.

Electrical Conductivity.—Specific conductivity values of the order of 10^{-6} ohm^{-1} cm.$^{-1}$ and above recorded on p. 2840 were determined by using a Mullard Measuring Bridge Type G.M. 4140/1, in conjunction with a Mullard Cell Type G.M. 4221. The cell was adapted as described in Part VI (*J.*, 1951, 1303), and a thermometer was incorporated in such a way that the bulb was immersed in the liquid near the electrodes. The conductivity of the 8·8% trioxide solution was obtained by using the condenser method described in Part III (*loc. cit.*).

Product of Reaction.—The product was obtained by immersing a block (about 5 g.) of A.R. zinc in about 15 ml. of 70% (wt./wt.) dinitrogen trioxide in dinitrogen tetroxide, contained in a 10 × 1·5 cm. tube fitted with a B.14 ground-glass joint and a phosphoric oxide guard tube, so that the gas space in the tube was kept dry and at atmospheric pressure. The contents of the tube were kept at −5° for about 10 hours, during which approximately 0·5 g. of product formed. During this period the initial volume of liquid was maintained, by the addition of further quantities of the liquid, although its trioxide content decreased to about 40%. The zinc block was then removed, the liquid decanted in a closed system, and the temperature allowed to rise to about 20°. On evaporation of the adhering liquid, the product remained as a finely-crystalline white powder.

Analysis of Reaction Product.—In the hydrolytic method, approximately 0·5 g. of product was sealed into a glass phial. The phial was immersed in a stout glass bottle containing an excess of 0·1N-sodium

hydroxide solution, and the minimum of air space, and was broken by shaking. The nitrite content of the resulting solution was determined by using standard potassium permanganate solution. It was observed that if there was any appreciable volume of air in the bottle above the solution, an acid spray formed in the air space; the estimated nitrite content was then low, owing to atmospheric oxidation of the nitrous acid in the spray.

Reactions with Sodium.—A piece (approx. 1 g.) of clean sodium was added to 20 ml. of a 70% solution of dinitrogen trioxide in the tetroxide. A reaction (more vigorous than with the tetroxide alone) ensued, and the metal became coated with a layer of white solid. The liquid was decanted, and the solid remaining was freed from oxides of nitrogen under slightly reduced pressure. The reaction product separated from the remaining sodium metal, was dissolved in dilute sodium hydroxide solution. This solution was found to contain sodium nitrate only; the complete absence of nitrite was confirmed by chemical methods, and from the ultra-violet absorption spectrum.

About 1 g. of pure sodium nitrite was added to 20 ml. of a solution of 40% dinitrogen trioxide in the tetroxide. After 10 hours the solid was freed from oxides of nitrogen, and analytical methods similar to those referred to above confirmed that the sodium nitrite was recovered unchanged.

THE UNIVERSITY, NOTTINGHAM. [*Received, May 3rd*, 1951.]

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631. *The Liquid Dinitrogen Tetroxide Solvent System. Part X.* The Reaction of Zinc with Liquid Nitrosyl Chloride–Dinitrogen Tetroxide Mixtures.*

By C. C. ADDISON and J. LEWIS.

Rates of reaction of metallic zinc with solutions of nitrosyl chloride in dinitrogen tetroxide have been determined at 0° over the 0—40% nitrosyl chloride concentration range. The rate of reaction in a nitrosyl chloride solution is less than in a solution of dinitrogen trioxide of equivalent concentration, although this position is probably reversed at high concentrations. Over the major portion of the concentration range the rate of reaction is proportional to the square of the nitrosyl chloride concentration, and measurement of the electrical conductivities of the solutions supports the deduction that reaction with zinc takes place on impact of nitrosyl chloride molecules (rather than NO^+ ions) at the metal surface. In the 0—10% concentration range the increase in rate of reaction is more rapid; this may be due to an increase in the rate of the zinc–dinitrogen tetroxide reaction in a medium of higher dielectric constant.

The product of reaction, at concentrations up to about 85%, is a mixture of the compounds $Zn(NO_3)_2,2N_2O_4$ and $ZnCl_2,NOCl$. Above 85% of nitrosyl chloride, only the latter compound is obtained. This arises from the operation of the equilibrium

$$Zn(NO_3)_2 + NOCl \rightleftharpoons ZnCl_2 + N_2O_4$$

Evidence for the formulation of the compound $ZnCl_2,NOCl$, in the dimeric form in which the zinc ion is 4-co-ordinated, is considered. This is correlated with the existence of a compound $ZnCl_2,NOCl,N_2O_4$, stable over a narrow range of temperature.

SOME preliminary experiments on the reaction between zinc and solutions of nitrosyl chloride in liquid dinitrogen tetroxide were reported in Part I (*J.*, 1949, S 211). The addition of nitrosyl chloride to the liquid tetroxide was observed to increase the rate of reaction, and two alternative mechanisms were postulated: (*a*) The addition of nitrosyl chloride may increase the concentration of NO^+ ions (the "solvent cations") and reaction may involve electron transfer from the zinc atom to the NO^+ ion. (*b*) Reaction may occur as a result of collision of NOCl molecules with the metal surface.

The experiments described below were carried out in an attempt to determine which of these two mechanisms is the more probable. The increase in reaction rates and electrical conductivity produced on addition of nitrosyl chloride are of the same order as those produced by equivalent concentrations of dinitrogen trioxide. However, the product of reaction involving dinitrogen trioxide is the same compound $Zn(NO_3)_2,2N_2O_4$ as is formed with the pure

* Part IX, preceding paper.

tetroxide, whereas the product of reaction with nitrosyl chloride solutions contains the compound $ZnCl_2,NOCl$, and the mechanisms of the two reactions appear to be quite different.

Results and Discussion.

Rate of Reaction.—The variation in rate of reaction of zinc with concentration of nitrosyl chloride is shown in Fig. 1 (curve *A*) for the 0—40% concentration range at 0°. The slope of curve *A* shows a continual increase with increasing nitrosyl chloride concentration, compared with the decreasing slope obtained in dinitrogen trioxide solutions (Part IX, preceding paper) and the curves for the two solutes are therefore different in character. In a solution of nitrosyl chloride of concentration 8 g.-mols./l., the rate of reaction is 5 times that with the pure tetroxide, compared with an 8-fold increase for a corresponding concentration of dinitrogen trioxide. The maximum concentration (about 40%) employed in the present measurements was determined by the stability of the liquid mixtures at 0°, but the form of the curves indicates that (under experimental conditions so adjusted that the full concentration range could be used) the rate of reaction with nitrosyl chloride solutions would exceed the rate with dinitrogen trioxide solutions at higher concentrations.

Fig. 1.

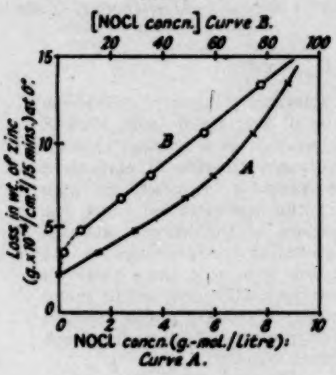
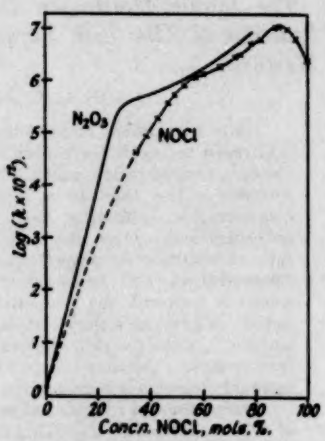


Fig. 2.



Curve *B* (Fig. 1) shows that linear relation exists between the rate of reaction and the square of the nitrosyl chloride concentration, for concentrations greater than about 2·4 g.-mols./l. (10%). The rate of reaction *R* may be represented by the expression

$$R = k[\mathrm{Zn}][\mathrm{NOCl}]^2 + k_1$$

The factor [Zn] is a constant since *R* is referred to unit area, and k_1 represents the contribution to the total rate of reaction made by the zinc–dinitrogen tetroxide reaction. In view of the linearity between *R* and $[NOCl]^2$, it appears that over the major portion of the concentration range it is unnecessary to consider as significant any mechanism other than that represented by the equations

$$\mathrm{Zn} + 2\mathrm{NOCl} \longrightarrow \mathrm{ZnCl_2} + 2\mathrm{NO} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

followed by

$$\mathrm{ZnCl_2} + \mathrm{NOCl} \longrightarrow \mathrm{ZnCl_2,NOCl}$$

Reaction is therefore considered to occur on impact of two nitrosyl chloride molecules at a zinc atom, rather than in a step-wise manner. In view of the experimental data, the reaction cannot be considered as occurring between the zinc atom and two NO^+ ions unless the degree of dissociation of the NOCl molecule into NO^+ and Cl^- ions is independent of nitrosyl chloride concentration. Such a condition is most unlikely in this system in view of the variation in dielectric constant of the medium with concentration.

At low concentrations (in the 0—2·4 g.-mol./l. range) represented by the broken portion of curve *B* (Fig. 1) the rate of reaction increases more rapidly than is required by equation (1).

There is no reason to doubt that the above mechanism is operative at low concentrations also, but in addition a further factor (which is either absent or negligible at high concentrations) increases the reaction rate by an amount which is clearly apparent at small reaction rates. Line *B*, when extrapolated, meets the rate axis at $3{\cdot}80 \times 10^{-4}$ g./cm.^{2}/15 minutes, compared with $2{\cdot}25 \times 10^{-4}$ for the zinc–pure tetroxide reaction. It is probable that the difference between these two rates finds explanation in the influence which the presence of nitrosyl chloride has on the zinc–tetroxide reaction. In Part VIII (*J.*, 1951, 2833) it has been postulated that this reaction takes place (at 0°) between zinc atoms and $[NO^+][NO_3^-]$ ion pairs. The equilibrium

$$N_2O_4 \rightleftharpoons 2NO_2 \rightleftharpoons [NO^+][NO_3^-] \rightleftharpoons NO^+ + NO_3^-$$

will be displaced towards the right-hand side by addition of a liquid which increases the dielectric constant of the medium. The dielectric constant of liquid nitrosyl chloride is 18·2 at 12° (Ketelaar, *Rec. Trav. chim.*, 1943, **62**, 289), and its addition to dinitrogen tetroxide ($\varepsilon = 2{\cdot}42$) will therefore result in an increase in the concentration of ion-pairs and/or free ions. Against this, any dissociation of nitrosyl chloride to give NO^+ and Cl^- ions would displace the above equilibrium to the left. In the case of nitrosyl chloride the net effect is a small displacement of the equilibrium to the right-hand side. When the two influences referred to above are complementary (as in the case of dinitrogen trioxide solutions) rather than opposed, a considerable increase in the rate of the zinc–dinitrogen tetroxide reaction results.

Reaction with Iron.—It is of interest to compare the behaviour of iron in nitrosyl chloride–dinitrogen tetroxide mixtures with that of zinc. Iron reacts very slowly with dilute solutions of nitrosyl chloride, but reaction is rapid in 50% solution. Although an accurate reaction rate–concentration curve corresponding to curve *A* (Fig. 1) has not been obtained for iron, observation of the reaction over a range of nitrosyl chloride concentration suggests that the curve would be of the same form as curve *A*, but would follow a cube rather than a square law with respect to concentration, as required by the reaction $Fe + 3NOCl = FeCl_3 + 3NO$.

Electrical Conductivities.—The specific conductivities of liquid mixtures of nitrosyl chloride and dinitrogen tetroxide (determined at −10°) are shown in Fig. 2. The specific conductivity of pure nitrosyl chloride was found to be $2{\cdot}73 \times 10^{-6}$ ohm^{-1} cm.$^{-1}$ at −10°, in good agreement with Burg and Campbell's value of $2{\cdot}88 \times 10^{-6}$ ohm^{-1} cm.$^{-1}$ at −20° (*J. Amer. Chem. Soc.*, 1948, **70**, 1964). The general form and position of the conductivity curve indicate that no appreciable ionisation takes place in the system. The small increase in conductivity which occurs on addition of dinitrogen tetroxide to nitrosyl chloride is probably due to ionisation of the tetroxide, but the maximum specific conductivity does not exceed 10^{-5} ohm^{-1} cm.$^{-1}$. Conductivity values for this system therefore support the deduction that the reaction of zinc takes place on impact with nitrosyl chloride molecules rather than with NO^+ ions produced by ionisation of the NOCl molecules. The conductivity curve for dinitrogen trioxide–tetroxide mixtures is superimposed in Fig. 2 for comparison. The curve is similar in form, and range, to the nitrosyl chloride curve, but the increase in conductivity on addition of the solute to the tetroxide is more rapid in the case of dinitrogen trioxide. This may reflect the relative dieletric constants of the trioxide and nitrosyl chloride.

Products of Reaction.—When zinc is added to a mixture of nitrosyl chloride and dinitrogen tetroxide, the simultaneous reactions occurring may be summarised as follows:

(*a*) $Zn + 2NOCl = ZnCl_2 + 2NO$
$ZnCl_2 + NOCl = ZnCl_2,NOCl$

(*b*) $Zn + 2N_2O_4 = Zn(NO_3)_2 + 2NO$
$Zn(NO_3)_2 + 2N_2O_4 = Zn(NO_3)_2,2N_2O_4$

Since the extrapolation of line *B* (Fig. 1) passes through the rate axis at a point above that representing the tetroxide reaction alone, it was to be expected that the product of reaction for mixtures of nitrosyl chloride and dinitrogen tetroxide of any composition would be a mixture of $ZnCl_2,NOCl$ and $Zn(NO_3)_2,2N_2O_4$. The product was obtained by adding a block of pure zinc (about 5 g.) to 20 ml. of the liquid at 0°. About 0·2—0·6 g. of product was formed in ten hours according to the concentration. The excess of liquid was decanted, the zinc block removed, and the nitrosyl chloride and dinitrogen tetroxide adhering to the solid were allowed to evaporate at room temperature; the product then remained as a very pale yellow crystalline mass. For nitrosyl chloride concentrations up to about 85%, the product was found to contain chloride and nitrate. When heated gently, the crystals evolved dinitrogen tetroxide, and softened to a yellow pasty mass. On being heated further, nitrosyl chloride was evolved, and when gas evolution ceased, the remaining solid was shown to be a mixture of zinc chloride and zinc nitrate. The properties of the product were therefore consistent with its formulation as a mixture of the compounds $ZnCl_2,NOCl$ and $Zn(NO_3)_2,2N_2O_4$. As the nitrosyl chloride content of the reaction

mixture increased within the 0—85% range, the proportion of $ZnCl_2$,NOCl in the product also increased; this is illustrated in the following table:

Initial NOCl concn. (%) in reaction mixture ...	0	13	36	45·4	78	90	100
Chloride content of product, %	0	19·8	28·2	27·0	44·3	52·7	52·7

Prolonged keeping of the reaction mixture during preparation of the product led to some decrease in the nitrosyl chloride content. This no doubt accounts for the slight discrepancies in the above table, but there is clearly a trend towards a high chlorine content in the product.

The product obtained from reaction mixtures containing more than about 85% of nitrosyl chloride could not be distinguished from the compound $ZnCl_2$,NOCl (chloride content 52·7%). There are two reasons for this. First, the proportion of this compound formed is a function of the square of the nitrosyl chloride concentration, so the proportion of nitrate formed will become very small. Secondly, the following reaction between products and reacting liquid can take place in either direction according to conditions:

$$Zn(NO_3)_2 + 2NOCl \rightleftharpoons ZnCl_2 + 2N_2O_4 \quad . \quad . \quad . \quad . \quad . \quad (2)$$

At high nitrosyl chloride concentrations, the equilibrium will be displaced to the right, and the zinc nitrate initially formed by reaction of zinc with the tetroxide will therefore be converted into chloride. In the dinitrogen tetroxide solvent system the forward reaction (equation 2) becomes an acid–base reaction, and the reverse reaction is an example of solvolysis. The validity of the equilibrium represented by equation (2) has been established as follows.

Zinc Nitrate–Nitrosyl Chloride Reaction.—About 1 g. of the crystalline compound $Zn(NO_3)_2.2N_2O_4$ was treated with 15 ml. of pure nitrosyl chloride for 1 hour at −10°. The temperature was then allowed to rise to about 20°; nitrosyl chloride and dinitrogen tetroxide evaporated, leaving a free-flowing white powder, which was shown to be the compound $ZnCl_2$,NOCl.

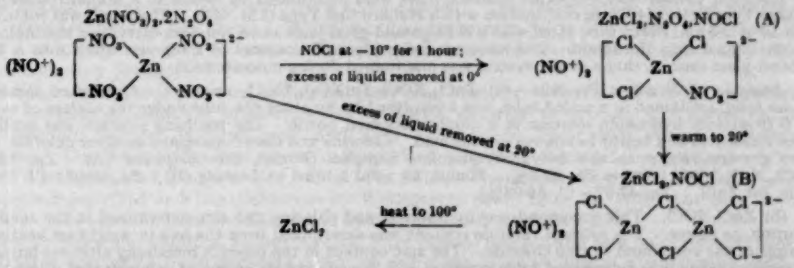
Zinc Chloride–Dinitrogen Tetroxide Reaction.—Pure zinc chloride was obtained from the compound $ZnCl_2$,NOCl by heating it to remove nitrosyl chloride. About 0·5 g. of zinc chloride was treated with 10 ml. of liquid dinitrogen tetroxide at 20°. The liquid rapidly developed a red coloration due to nitrosyl chloride. After several hours the liquid was allowed to evaporate, and the resulting solid product analysed. The chlorine content was 11·93%; the product at this stage being assumed to be a mixture of the compound $ZnCl_2$,NOCl and $Zn(NO_3)_2.2N_2O_4$, this chlorine content is equivalent to a zinc content of 20·96%. Analysis gave Zn, 21·16%. By this single treatment approximately half of the chlorine originally present as zinc chloride was removed as nitrosyl chloride. Successive treatments with dinitrogen tetroxide reduced the chlorine content of the product, and after six such treatments the product was converted completely into the compound $Zn(NO_3)_2.2N_2O_4$. A similar reaction took place when the compound $ZnCl_2$,NOCl was employed instead of zinc chloride.

The above experiments indicate that, although equation (2) is completely reversible under appropriate conditions, the forward (or acid–base reaction) occurs more completely than the reverse (or solvolytic) reaction. The equilibrium (equation 2) favours the formation of zinc chloride, and in consequence the product obtained from mixtures containing a high concentration of nitrosyl chloride contains no detectable quantity of nitrate.

Structure of the Compound $ZnCl_2$,NOCl.—The empirical formula for this compound, first determined by Sudborough (*J.*, 1891, **59**, 655), has been confirmed by Asmussen (*Z. anorg. Chem.*, 1939, **243**, 127), by Partington and Whynes (*J.*, 1948, 1952), and in the present work. Asmussen regards the compound as a loose addition compound (analogous to $HgCl_2$,NOCl and $AlCl_3$,NOCl), since nitrosyl chloride may be removed as such by gentle heat. However, the $ZnCl_2$: NOCl ratio of 1 : 1 is so clearly defined that it is permissible to consider a possible structure for the compound. The more stable addition compounds of metallic chlorides with nitrosyl chloride have for some time been accepted as nitrosyl compounds; Klinkenberg (*Rec. Trav. chim.*, 1937, **56**, 749; *Chem. Weekblad*, 1938, **35**, 197) has shown by crystallographic methods that the compounds $SnCl_4.2NOCl$ and $PtCl_4.2NOCl$ are isomorphous with $(NH_4)_2[SnCl_6]$ and $(NH_4)_2[PtCl_6]$ respectively, and should therefore be formulated as $(NO^+)_2[SnCl_6]^{2-}$ and $(NO^+)_2[PtCl_6]^{2-}$. The formulation of the compound $ZnCl_2$,NOCl as a nitrosyl compound should not be dismissed on the grounds of lower stability alone, since it is well known that the stability of co-ordination complexes varies widely with the metal involved. The compound $AlCl_3$,NOCl is of a lower order of stability than the corresponding platinum and tin compounds, and is dismissed by Asmussen (*loc. cit.*) as a loose addition compound, but Burg and Campbell (*loc. cit.*) have observed this compound to be a strong electrolyte in solution in pure nitrosyl chloride, and

formulate it as $(NO^+)[AlCl_4]^-$. The stability of the compound $ZnCl_2,NOCl$ is of a similar order to that of the aluminium compound. However, the formulation of the complexes mentioned above as nitrosyl salts of chloro-complexes involves the use of co-ordination numbers for aluminium, tin, and platinum which are known to be characteristic of these metals; the corresponding structure for the zinc complex, *i.e.*, $(NO^+)[ZnCl_3]$, involves 3-co-ordination, whereas the formation of two linear *s–p* bonds, or four tetrahedral sp^3 bonds is predominant in the co-ordination chemistry of zinc. Many compounds of empirical formula $MZnCl_3$ are known, where M is a univalent metal ion. Since M may also be $\frac{1}{2}Mg$ or $\frac{1}{2}Ba$ (Partington, "General and Inorganic Chemistry," Macmillan, 1947, p. 388), these solids are to be considered as composed of essentially ionic crystals, or in the dimeric form $M_2[Zn_2Cl_4]$. The former appears to be the more probable alternative for these metal salts, but the chemistry of the compound $ZnCl_2,NOCl$ provides some evidence for considering that the zinc is in a 4-co-ordinate complex, and therefore that the molecule may be a dimer.

In the zinc nitrate–nitrosyl chloride reaction discussed above, the warming of the reaction mixture from −10° to 20° resulted in the formation of the compound $ZnCl_2,NOCl$. If this warming is carried out slowly, it is possible to detect an intermediate stage. The reactions are summarised below.



The removal of excess of liquid at 0° gave compound (A) as a very pale yellow, free-flowing powder, which was stable provided that the atmosphere of nitrosyl chloride and dinitrogen tetroxide was maintained. When the temperature was increased to about 20°, dinitrogen tetroxide (containing no more than a trace of nitrosyl chloride) was evolved, leaving compound (B). Compounds (A) and (B) were almost identical in appearance. The solid formed on heating (B) until evolution of nitrosyl chloride ceased was shown to be pure zinc chloride. In view of the ready evolution of dinitrogen tetroxide, (A) may be a simple lattice compound. On the other hand, when it is formulated as a nitrosyl compound as shown, the zinc ion is 4-co-ordinated, and the 4-co-ordination may be maintained on evolution of the tetroxide by representing compound (B) in the dimeric form as shown.

Burg and Campbell (*loc. cit.*) have shown that mononitrosyl salts (*e.g.*, $NO[AlCl_4]$, $NO[SbCl_6]$, and $NO[FeCl_4]$) are readily soluble in liquid nitrosyl chloride, whereas those dinitrosyl salts tested, $(NO)_2[SnCl_6]$ and $(NO)_2[TiCl_6]$, are quite insoluble. It is relevant that both compounds (A) and (B) are insoluble in liquid nitrosyl chloride, which is consistent with their formulation as dinitrosyl salts.

Experimental.

Preparation of Nitrosyl Chloride and Nitrosyl Chloride–Dinitrogen Tetroxide Mixtures.—These were prepared precisely as described in Part II (*J.*, 1949 S 218). The use of phosphoric oxide as a drying agent for nitrosyl chloride has been found to be undesirable unless the condensed product is given further purification by fractional distillation. When the calcium chloride drying tubes were replaced by a phosphoric oxide drying train, the nitrosyl chloride vapour appeared to react with the phosphoric oxide. Nitric oxide was produced, which dissolved in the condensed nitrosyl chloride, converting the colour of the liquid from blood-red to black.

Composition of Mixtures.—The composition of the reaction mixtures used was determined from the m. p., the liquidus curve given in Fig. 3, Part II (*loc. cit.*), being used. In the measurements of rate of reaction with zinc, the m. p. of the liquid was determined before and after each experiment. Since the b. p. of nitrosyl chloride (−5·5°) is appreciably higher than that of dinitrogen trioxide (−27·3°), solutions of nitrosyl chloride were more stable than solutions of the trioxide (see Part IX, preceding paper).

Rate of Reaction.—The experimental technique employed has been described in Part VIII (*loc. cit.*). Since preliminary experiments showed that the quantity of zinc reacting, per unit area, was propor-

tional to the time of immersion during the first 15 minutes, rates of reaction recorded in Fig. 1 were determined for 15-minute immersion periods.

The reaction between zinc and dinitrogen tetroxide involves active species which are in equilibrium with the tetroxide (Part VIII, *loc. cit.*); provided that the metal surface is " wetted " by the tetroxide, the active species has direct access to the surface, and a stirring rate of 40 r.p.m. was found to be sufficient to disperse the trioxide produced by reaction. Similar conditions apply to dinitrogen trioxide–tetroxide mixtures (preceding paper). However, if the reaction with nitrosyl chloride solution involves impact of nitrosyl chloride molecules at the metal surface, it appeared possible that the products of reaction might present a barrier to the diffusion of nitrosyl chloride to the surface. The influence of stirring rate on the rate of reaction of zinc is given in the following table; the measurements were carried out at 0°, a 40·1% solution of nitrosyl chloride in dinitrogen tetroxide being used :

Stirring rate (revs. per min.)	0	10	108	150	250
Rate of reaction of zinc (g. × 10^{-4}/cm.^{2}/15 mins.)	8·4	9·0	13·5	13·5	13·3

The rate of reaction increases at first with increase in rate of stirring, whereas a decrease occurs with pure tetroxide. At stirring rates above 100 r.p.m. the rate of reaction is independent of stirring rate, and diffusion is not significant. The measurements recorded in Fig. 1 were carried out at 250 r.p.m.

Briner and Pylkoff's data (*J. Chim. physique*, 1912, **10**, 640) were used in the calculation of the density of NOCl–N_2O_4 mixtures.

Electrical Conductivity.—Specific conductivities were determined by means of a Mullard Measuring Bridge Type G.M. 4140/1, in conjunction with a Mullard Cell Type G.M. 4221. The liquid was contained in a 10 × 2·5 cm. Pyrex tube fitted with a B.24 ground-glass joint and a side-arm carrying a thermometer which dipped into the liquid. The electrode assembly (cell constant = 2·46) was fitted into a B.24 ground-glass cone, so that a closed system was maintained during measurement.

Analysis of Reaction Products.—(a) $ZnCl_2$,NOCl–$Zn(NO_3)_2$,$2N_2O_4$ *mixtures.* A weighed quantity of the solid, contained in a sealed tube, was hydrolysed by breaking the tube under the surface of excess of 0·1N-sodium hydroxide solution in a stout, stoppered bottle. The resulting solution was acidified with nitric acid and boiled to remove nitrous acid. Chlorine was then determined as silver chloride, and zinc gravimetrically as the 8-hydroxyquinoline complex [Found, for *compound* (A): Zn, 22·68. $ZnCl_2$,N_2O_4,NOCl requires Zn, 22·3%. Found, for solid formed on heating (B): Zn, 48·02; Cl, 52·25. Calc. for $ZnCl_2$: Zn, 47·97; Cl, 52·03%].

(b) ZnCl,NOCl. This compound was hydrolysed, and chlorine and zinc determined in the acidified solution, as above. The nitrosyl chloride content was determined from the loss in weight on heating a sample of the compound to zinc chloride. The zinc content in the product remaining after evolution of nitrosyl chloride was determined by conversion into the nitrate by means of concentrated nitric acid, followed by ignition to zinc oxide [Found for compound (B): Zn, 32·2. Calc. for $ZnCl_2$,NOCl: Zn, 32·4%].

THE UNIVERSITY, NOTTINGHAM. [*Received, May 3rd*, 1951.]

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632. *The Chemistry of Fluorene. Part I. Condensations with 9-Fluorenylsodium.*

By E. J. GREENHOW, E. N. WHITE, and D. MCNEIL.

A convenient method for the preparation of 9-fluorenylsodium is described. Condensation of 9-fluorenylsodium with methyl iodide or sulphate, ethyl bromide or sulphate, allyl chloride, benzyl chloride, or ethylene dichloride gives the corresponding 9-substituted fluorene in good yield; with ethylene dibromide a low yield of difluorenylethane is obtained. 2 : 2′-Dichlorodiethyl ether gives 2-chloroethyl 2-9′-fluorenylethyl ether which on dehydrohalogenation yields fluorene-9-*spiro*-4′-tetrahydropyran. Ethylene chlorohydrin gives fluorene and 9-2′-hydroxyethylfluorene. No condensation occurred with vinyl chloride or bromide.

9-ALKYLFLUORENES are generally prepared by condensing an alkyl halide with (*a*) a 9-acylfluorene in the presence of sodium ethoxide (Brown and Bluestein, *J. Amer. Chem. Soc.*, 1943, **65**, 1084; Wislicenus and Mocker, *Ber.*, 1913, **46**, 2783), (*b*) 9-fluorenyl-lithium, or (*c*) 9-fluorenylmagnesium bromide (Miller and Bachman, *J. Amer. Chem. Soc.*, 1935, **57**, 766). The last method does not always yield the desired product; for example, benzyl bromide gives a mixture of dibenzyl and di-9-fluorenyl.

Failure hitherto to use 9-fluorenylsodium for such preparations is due to the absence of an easy method for its preparation reasonably pure in good yield. Patented methods involve high-temperature fusion of fluorene with sodium (Weissgerber, G.P. 209,432) or sodamide (Weissgerber, G.P. 203,312) but the product is of doubtful purity and in a form unsuited for the further reaction. Zeigler and Jakob (*Annalen*, 1934, **511**, 55) suggest that 9-fluorenylsodium is formed when fluorene is heated with finely divided sodamide in boiling ether but, according to Miller and Bachman (*loc. cit.*), no reaction is observed when these reagents are heated under reflux in xylene. According to Lebeau and Picon (*Compt. rend.*, 1921, **173**, 84) the reaction of fluorene, sodium, and ammonia under pressure yields disodiofluorene with reduction of part of the fluorene by the hydrogen liberated.

The only 9-monosubstituted fluorenes hitherto prepared by the use of 9-fluorenylsodium are fluorene-9-carboxylic acid and 9-diphenylmethylfluorene (Schlenk and Bergman, *Annalen*, 1928, **463**, 188). In these cases the sodio-derivative was formed by the action of triphenylmethylsodium, involving a tedious preparation and separation.

We have found that 9-fluorenylsodium can be prepared in good yield and in a sufficiently pure form from powdered sodamide and fluorene in boiling decahydronaphthalene, fluorenylsodium being deposited as a brownish-yellow powder. If excess of fluorene is used there is little chance of any disodium derivative being formed. The temperature and the nature of the solvent appear to be critical. In boiling light petroleum (b. p. 100—120°), less than 5% of the sodamide reacts in 18 hours. Methylnaphthalene and tetrahydronaphthalene yield a less satisfactory product.

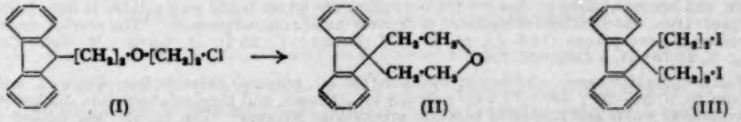
9-Fluorenylsodium, prepared in this manner, reacts readily with methyl iodide or sulphate, ethyl bromide or sulphate, allyl chloride, or benzyl chloride to produce the corresponding 9-substituted fluorene in good yield and with little or no by-product except unchanged fluorene. Our 9-benzylfluorene agrees in properties with that described by previous workers (*e.g.*, Wislicenus and Mocker, *Ber.*, 1913, **46**, 2772; Vansheidt, *Ber.*, 1931, **64**, 917). The compound described as 9-benzylfluorene by Weissgerber (*Ber.*, 1901, **34**, 1659) was later shown to be 9 : 9-dibenzylfluorene by Thiele and Henle (*Annalen*, 1906, **347**, 299).

9-Ethylfluorene, obtained by our method after careful purification as a colourless oil, slowly deposits a crystalline hydroperoxide which on reduction gives an almost quantitative yield of 9-ethylfluoren-9-ol. The ready formation of this stable hydroperoxide may explain why 9-ethylfluoren has been variously described as an uncrystallisable oil and as a solid of m. p. 105—108° (Wislicenus and Densch, *Ber.*, 1902, **35**, 759; Wislicenus and Mocker, *loc. cit.*, p. 2781; Meerwein, *Annalen*, 1913, **396**, 244; Zelinsky and Gawerdowskaja, *Ber.*, 1928, **61**, 1052; Miller and Bachman, *loc. cit.*); the product isolated by Wislicenus and Densch was however later shown (Wislicenus and Mocker, *loc. cit.*, p. 2773) to be impure fluorene.

Ethylene dichloride reacts with 9-fluorenylsodium to give a moderate yield of the expected 9-2′-chloroethylfluorene, but ethylene dibromide even in considerable excess gives only difluorenylethane in poor yield.

When 9-fluorenylsodium is refluxed with ethylene chlorohydrin in light petroleum a considerable amount of fluorene is precipitated, but a small amount of 9-2′-hydroxyethylfluorene can be isolated from the reaction product.

With 2 : 2′-dichlorodiethyl ether an excellent yield of 2-chloroethyl 2-9′-fluorenylethyl ether was obtained, which on dehydrohalogenation by solid sodium hydroxide at 200° is converted into fluorene-9-*spiro*-4′-tetrahydropyran (II). The structure of the spiran was confirmed



(I) (II) (III)

by its ultra-violet absorption spectrum which shows it to contain the fluorene nucleus (see table, p. 2851), and by reaction with phosphoric acid–potassium iodide to give a product having the iodine content required for 9 : 9-di-2′-iodoethylfluorene (III).

When vinyl chloride or bromide is heated with 9-fluorenylsodium under pressure the products are fluorene, acetylene, and the sodium halide. Failure of these condensations is not surprising since the initial ionisation of the halogen atom is prevented by the neighbouring double bond. The low yields with ethylene dihalides may well be caused by dehydrohalogenation to vinyl halides with the formation of fluorene and sodium chloride.

Experimental.

Ultra-violet absorption spectra were determined in absolute ethanol, with a Hilger "Uvispek" spectrophotometer. We are indebted to Mr. W. G. Wilman for the measurements.

The fluorene (North Thames Gas Board) was recrystallised from light petroleum. The sodamide was purchased as a powder from Messrs. May and Baker Ltd. All m. p.s are uncorrected.

9-*Fluorenylsodium*.—Fluorene (183 g.), powdered sodamide (39 g.), and decahydronaphthalene (dried over sodium) (400 c.c.) were heated at the b. p. for 4 hours, with stirring, in an atmosphere of nitrogen. The hot solution was filtered and the brownish-yellow 9-fluorenylsodium (200 g.) washed with hot decahydronaphthalene and finally with hot light petroleum (b. p. 100—120°) (Found: Na, 12·3. Calc. for $C_{13}H_9Na$: Na, 12·2%).

9-*Methylfluorene*.—(*a*) 9-Fluorenylsodium (100 g.), methyl iodide (150 c.c.), and light petroleum (b. p. 40—60°) (200 c.c.) were refluxed for 12 hours. The product was filtered to remove the sodium iodide which was formed in quantitative amount, and the filtrate evaporated on a water-bath to recover the unchanged methyl iodide, finally under reduced pressure. The oily residue was fractionated *in vacuo*. The main fraction, b. p. 160—170°/24 mm. (85·1 g.), solidified on storage and crystallised from light petroleum (b. p. 40—60°) as prisms, m. p. 45—47° (Found: C, 92·7; H, 6·9%; *M*, 179. Calc. for $C_{14}H_{12}$: C, 93·3; H, 6·7%; *M*, 180).

(*b*) 9-Fluorenylsodium (65 g.), methyl sulphate (80 c.c.), and benzene (200 c.c.) were kept overnight at room temperature and then filtered from sodium methyl sulphate (quantitative amount), and the filtrate was refluxed on a water-bath for 2 hours with sodium hydroxide solution (40%; 120 c.c.). The benzene layer was washed with water, dilute hydrochloric acid, and finally sodium carbonate solution. Evaporation of the dried benzene solution left a red oil which solidified on cooling. 9-Methylfluorene, crystallised as above, had m. p. 45—46° (49 g.).

9-*Ethylfluorene*.—(*a*) 9-Fluorenylsodium (188 g.), ethyl bromide (200 c.c.), and light petroleum (b. p. 40—60°; 200 c.c.) were refluxed for 20 hours, and the product was filtered. The filtrate was evaporated and the oily residue distilled under reduced pressure. The fraction boiling at 180—200°/14 mm. (153 g.) was cooled in a refrigerator for 2 days and deposited 10 g. of fluorene which were removed by filtration. The filtrate, after distillation at 135° in superheated steam, was fractionated in a vacuum through a column of 20 theoretical plates. A colourless oil (112 g.) distilled at 156—158°/12·5 mm. and had n_D^{28} 1·6135 (Found: C, 92·55; H, 7·2%; *M*, 195. Calc. for $C_{15}H_{14}$: C, 92·8; H, 7·2%; *M*, 194). The structure of this compound was confirmed by its oxidation with lead oxide to 9-ethylidenefluorene, and to acetaldehyde and fluorenone with sodium dichromate in acetic acid.

(*b*) 9-Fluorenylsodium (65 g.), ethyl sulphate (80 c.c.), and benzene (200 c.c.) were kept overnight at room temperature. The product was filtered to remove the sodium ethyl sulphate, and the filtrate evaporated on a water-bath at reduced pressure. The residual oil, fractionated *in vacuo*, gave 9-ethylfluorene, b. p. 163—166°/15 mm. (61 g.) (Found: C, 92·6; H, 7·2%).

9-*Ethylfluorenyl 9-Hydroperoxide*.—On storage in daylight, with access to air, 9-ethylfluorene was gradually converted into solid 9-*ethylfluorenyl 9-hydroperoxide* (approx. 20% in 6 months). This was precipitated free from unchanged 9-ethylfluorene by addition of light petroleum (b. p. 40—60°); it crystallised from benzene as prisms, m. p. 106·5—107·5° (Found: C, 79·25; H, 6·3; peroxide-O, 7·3. $C_{15}H_{14}O_2$ requires C, 79·5; H, 6·2; peroxide-O, 7·1%). (Peroxide-oxygen was determined by titration of the iodine liberated from potassium iodide in methanol-acetic acid with 0·1N-sodium thiosulphate). On reduction with potassium iodide in methanol, iodine was liberated and 9-ethylfluorenol, m. p. 101°, was formed.

9-*Allylfluorene*.—9-Fluorenylsodium (60 g.) and allyl chloride (200 c.c.) were refluxed for 2 hours, then cooled, and the sodium chloride filtered off. The filtrate was evaporated on the water-bath to yield crude 9-allylfluorene as a dark oil (67 g.), which was fractionated through a packed column as above. A small quantity of fluorene and a main fraction (62·3 g.) of 9-allylfluorene, b. p. 154—158°/11 mm., n_D^{28} 1·6165, were obtained (Found: C, 93·1; H, 6·9%; *M*, 207. Calc. for $C_{16}H_{14}$: C, 93·2; H, 6·8%; *M*, 206). Oxidation with sodium dichromate in acetic acid yielded fluorenone.

9-*Benzylfluorene*.—9-Fluorenylsodium (100 g.), benzyl chloride (200 c.c.), and light petroleum (b. p. 60—80°; 200 c.c.) were refluxed for 20 hours and then cooled; water was added to dissolve the sodium chloride, and benzene added to dissolve the benzylfluorene which is not very soluble in light petroleum. The organic layer was dried and evaporated to dryness under reduced pressure. The residue, crystallised from benzene, gave prisms (75·3 g.), m. p. 135° (Found: C, 93·9; H, 6·3%; *M*, 248. Calc. for $C_{20}H_{16}$; C, 93·75; H, 6·25%; *M*, 256).

9-2′-*Hydroxyethylfluorene*.—9-Fluorenylsodium (188 g.), ethylene chlorohydrin (400 c.c.), and light petroleum (b. p. 60—80°; 400 c.c.) were refluxed for 20 hours, and the cooled solution diluted with an equal volume of water and filtered to separate precipitated fluorene. The filtrate was diluted with a large excess of water, and the solid crude 9-2′-*hydroxyethylfluorene* was filtered off (45 g.). The filtrate was separated into an aqueous and an organic layer; the latter on evaporation yielded a further quantity of fluorene (total 110 g.). 9-2′-Hydroxyethylfluorene, crystallised from light petroleum (b. p. 60—80°) and then from benzene, formed needles, m. p. 101° (43 g.) (Found: C, 85·3; H, 6·7%; *M*, 216. $C_{15}H_{14}O$ requires C, 85·5; H, 6·65%; *M*, 210). Von Braun and Anton (*Ber.*, 1929, **62**, 145), by the Ladenburg reduction of ethyl fluorenylacetate, obtained a compound as a "thick uncrystallisable oil" which they regarded as 9-2′-hydroxyethylfluorene.

s-*Di*-9-*fluorenylethane*.—9-Fluorenylsodium (56 g.) was heated under reflux with ethylene dibromide (200 c.c.) for 6 hours and, after filtration, the reaction mixture was freed from unchanged ethylene dibromide by evaporation *in vacuo*. When the oily residue was diluted with light petroleum (b. p.

100—120°) a white solid (14 g.) was precipitated. On recrystallising this from benzene, *s*-di-9-fluorenylethane was obtained as prisms, m. p. 226° (Found: C, 93·6; H, 6·1. Calc. for $C_{28}H_{22}$: C, 93·75; H, 6·1%).

9-2′-*Chloroethylfluorene*.—Ethylene dichloride (400 c.c.) and 9-fluorenylsodium (110 g.) were refluxed for 17 hours, the mixture, when cool, was filtered, and the excess of ethylene dichloride evaporated on the water-bath at 15 mm. Crude 9-2′-*chloroethylfluorene*, obtained as a brown oil (118 g.), was purified by vacuum-distillation, to give unchanged fluorene (53 g.) and a fraction, b. p. 135—146°/2 mm. (Found: Cl, 11%). Further purification was difficult but freezing and recrystallisation several times from light petroleum (b. p. 40—60°) gave a pure product as prisms, m. p. 41—41·5° (Found: C, 78·65; H, 5·7; Cl, 15·4. $C_{15}H_{13}Cl$ requires C, 78·6; H, 5·7; Cl, 15·5%).

2-*Chloroethyl* 2-9′-*Fluorenylethyl Ether*.—9-Fluorenylsodium (110 g.) and 2 : 2′-dichlorodiethyl ether (400 c.c.) were refluxed for 6 hours, and the sodium chloride produced was filtered off from the hot solution. Excess of dichlorodiethyl ether was removed from the filtrate by vacuum-distillation and the residue, a viscous oil (142 g.), purified by vacuum-fractionation. The *2-chloroethyl 2-9′-fluorenylethyl ether* was finally obtained as a pale yellow oil, b. p. 197—199°/7·5 mm. (83 g.) (Found: Cl, 12·9%; *M*, 270. $C_{17}H_{17}OCl$ requires Cl, 13·0%; *M*, 272·5).

Fluorene-9-spiro-4′-*tetrahydropyran*.—2-Chloroethyl 2-9′-fluorenylethyl ether (5 g.) was heated with solid potassium hydroxide (1·5 g.) for 4 minutes at 270°. The solid product was washed with water and crystallised from propanol; it formed flat needles, m. p. 201° (4·1 g.), of *fluorene*-9-spiro-4′-*tetrahydropyran* (Found: C, 86·3; H, 6·8%; *M*, 232. $C_{17}H_{16}O$ requires C, 86·3; H, 6·8%; *M*, 236). Absorption spectra of this and the following compound, and of fluorene, are recorded in the table.

Fluorene	λ, Å	2260 *	2610	2885	3000
	log ε	3·86	4·24	3·78	3·94
Fluorene-9-*spiro*-4′-tetrahydropyran	λ, Å	2280	2670	2900	3010
	log ε	3·78	4·24	3·77	3·94
9 : 9-Di-2′-iodoethylfluorene	λ, Å	2300	2680	2910	3030
	log ε	3·91	4·23	3·74	3·88

* Inflection.

9 : 9-*Di*-2′-*iodoethylfluorene*.—Fluorene-9-*spiro*-4′-tetrahydropyran (1·3 g.) was added to potassium iodide (17·6 g.), 89% phosphoric acid (7·2 ml.), and phosphoric oxide (3·5 g.). The mixture was heated for 3 hours in an oil-bath, with stirring, under reflux, the temperature being raised from 80° to 130°, and kept at 95—100° for approx. 1½ hours. The cooled mixture was diluted with water and extracted with ether. The ethereal layer was decolourised with sodium thiosulphate solution, washed with sodium chloride solution and water, and dried ($MgSO_4$). On evaporation of the ethereal solution, an oil remained which was dissolved in benzene and chromatographed through alumina (8″ × ½″) which was eluted with benzene. Unchanged spiran was retained more strongly than was the iodo-compound, giving a fairly sharp separation. Final traces of the spiran were washed from the column with chloroform. 1·56 g. of iodo-compound (m. p. 174—178°) were obtained and 0·51 g. of unchanged starting material. The 9 : 9-*di*-2′-*iodoethylfluorene*, on recrystallisation from light petroleum (b. p. 80—100°), had m. p. 181·5—182° (prisms) (Found: C, 42·7; H, 3·4; I, 53·3%; *M*, 479. $C_{17}H_{14}I_2$ requires C, 43·0; H, 3·4; I, 53·6%; *M*, 474).

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The Coal Tar Research Association,
Oxford Road, Gomersal, near Leeds.

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633. isoQuinolines. *Part III.* The Nitration of* 3 : 4-*Dihydro- and* 1 : 2 : 3 : 4-*Tetrahydro-*iso*quinolines.*

By A. McCoubrey and David W. Mathieson.

Nitration of 3 : 4-dihydro- and 1 : 2 : 3 : 4-tetrahydro-*iso*quinoline is shown to lead to substitution in position 7. The hitherto unknown 7-nitro-*iso*quinoline has been prepared.

It has been shown (McCoubrey and Mathieson, *J.*, 1949, 696; McCoubrey, *J.*, 1950, 1833) that nitration of 3 : 4-dihydro-1-phenyl*iso*quinoline derivatives leads to introduction of a nitro-group at position 7. It appeared possible therefore that nitration and subsequent dehydrogenation of 3 : 4-dihydro- or 1 : 2 : 3 : 4-tetrahydro-*iso*quinoline might afford a route to the hitherto unknown 7-nitro*iso*quinoline.

* Part II, *J.*, 1950, 1833.

Treatment of 3 : 4-dihydro*iso*quinoline with sulphuric acid–potassium nitrate gave a nitro-compound, presumably 3 : 4-dihydro-7-nitro*iso*quinoline, which was dehydrogenated, without further purification, over palladium black in decalin. The product was shown to be 7-nitro*iso*quinoline by catalytic reduction of the nitro-group, to give 7-amino*iso*quinoline, identical with a sample synthesised by Robinson's method (*J. Amer. Chem. Soc.*, 1947, **69**, 1939) and kindly supplied by Dr. M. Kulka. The acetyl derivative had the melting point reported by Manske and Kulka (*Canad. J. Res.*, 1949, **27**, *B*, 161) for 7-acetamido*iso*quinoline. Finally, the ultra-violet absorption characteristics of the two samples of 7-amino*iso*quinolines were identical.

Under similar conditions, tetrahydro*iso*quinoline gave a mononitro-derivative from which catalytic reduction readily afforded the corresponding aminotetrahydro*iso*quinoline. Dehydrogenation of the nitro-compound under a variety of conditions failed to give a pure product and the structure was demonstrated indirectly. 2-Benzoyltetrahydro-nitro*iso*quinoline, obtained by benzoylation of the above nitration product, was reduced in two stages, first catalytically in the presence of Raney nickel to give amino-2-benzoyltetrahydro*iso*quinoline and, secondly, with lithium aluminium hydride to amino-2-benzyltetrahydro*iso*quinoline. The last product was identical with 7-amino-2-benzyltetrahydro*iso*quinoline synthesised by Mann and Beeby's method (*J.*, 1949, 1799). Thus 2-2′-chloroethyl-5-nitrobenzyl chloride and benzylamine afforded 2-benzyl-1 : 2 : 3 : 4-tetrahydro-7-nitro*iso*quinoline which was reduced catalytically to the corresponding amino-derivative. Furthermore, nitration of 2-benzyltetrahydro*iso*quinoline yielded 2-benzyl-7-nitrotetrahydro*iso*quinoline, indicating that *N*-alkylation had no influence on the point of entry of the nitro-group, a conclusion which is supported by the observation below. Nitration of 2-*n*-butyltetrahydro*iso*quinoline gave a nitro-derivative, the hydrochloride of which had a similar melting point to that of the 2-*n*-butyl-7-nitrotetrahydro*iso*quinoline hydrochloride described by Mann and Beeby (*loc. cit.*), but a mixed melting point with a sample kindly supplied by Dr. Mann did not afford unequivocal evidence of identity owing to the range of melting point over which both materials melted.

Experimental.

All hydrogenations were effected at atmospheric pressure and room temperature.

7-Nitroisoquinoline.—3 : 4-Dihydro*iso*quinoline (Decker, Kropp, Hoyer, and Becker, *Annalen*, 1913, **395**, 308) (600 mg.) in sulphuric acid (*d* 1·84; 2·5 c.c.) was added to potassium nitrate (500 mg.) in sulphuric acid (*d* 1·84; 2·5 c.c.), the temperature being kept at 0°. The mixture was allowed to attain room temperature during 2 hours and then warmed to 60° for 4 hours. The product was poured on ice; neutralisation with ammonia solution gave a light brown material (700 mg.), m. p. 88—90° (softens at 40° and resolidifies at ~45°). Dehydrogenation was effected by refluxing this compound in decalin (10 c.c.) for 2 hours with palladium black (200 mg.). The solution was filtered, diluted with its own volume of chloroform, and extracted with 2*N*-hydrochloric acid. Solid potassium hydroxide was cautiously added, with ice-cooling, a light brown crystalline mass (170 mg.) being obtained, m. p. 155—160°. This was sublimed at 180°/20 mm. and crystallised from light petroleum (b. p. 100—120°), giving *7-nitroisoquinoline* in colourless needles, m. p. 177—178° (Found: C, 62·5; H, 3·5; N, 15·9. $C_9H_6O_2N_2$ requires C, 62·1; H, 3·4; N, 16·1%).

7-Aminoisoquinoline.—7-Nitro*iso*quinoline (50 mg.) in ethanol (10 c.c.) was shaken with hydrogen in the presence of palladised charcoal (30%; 100 mg.). 26 c.c. of hydrogen were absorbed during 20 minutes. The solution was filtered and evaporated. The residue (45 mg.) crystallised from benzene–light petroleum (b. p. 60—80°) in prisms, m. p. 201—202° alone or in admixture with a specimen kindly supplied by Dr. M. Kulka. The acetyl derivative, made in the usual manner, had m. p. 148—149°. Manske and Kulka (*loc. cit.*) cite m. p. 147—148°.

1 : 2 : 3 : 4-Tetrahydro-7-nitroisoquinoline.—Tetrahydro*iso*quinoline (10·5 g.) (Wegler and Frank, *Ber.*, 1937, **70**, 1279) was converted into the sulphate by dissolution in the theoretical amount of 5*N*-sulphuric acid and evaporation to dryness. The powdered residue was added to a solution of potassium nitrate (10 g.) in sulphuric acid (*d* 1·84; 50 c.c.) with ice cooling and, after being kept overnight at room temperature, the whole was poured on ice and cautiously neutralised with aqueous ammonia. The base was extracted with chloroform and dried (K_2CO_3), and the chloroform removed at room temperature under reduced pressure. The residue was extracted with hot light petroleum (b. p. 60—80°), and the extract evaporated under reduced pressure at room temperature. The free base was unstable, especially in the presence of alkali, and was converted into the *hydrochloride* (12·5 g.) which crystallised from aqueous acetone in prisms, m. p. 261° (Found: N, 13·4; Cl, 16·6. $C_9H_{10}O_2N_2$,HCl requires N, 13·1; Cl, 16·6%). The *picrate* crystallised from acetone in large brown prisms, m. p. 190—192° (Found: N, 17·0. $C_9H_{10}O_2N_2$,$C_6H_3O_7N_3$ requires N, 17·2%). The *p-nitrobenzoyl* derivative crystallised from ethanol in yellow prisms, m. p. 209—210° (Found: N, 12·7. $C_{14}H_{12}O_5N_2$ requires N, 12·8%). The *benzoyl* derivative crystallised from alcohol in yellow plates, m. p. 125° (Found: N, 10·2. $C_{16}H_{14}O_2N_2$ requires N, 9·9%).

7-Amino-1 : 2 : 3 : 4-tetrahydroisoquinoline.—Tetrahydro-7-nitro*iso*quinoline hydrochloride (5 g.) in ethanol (150 c.c.) was shaken with hydrogen in the presence of platinum oxide (300 mg.). 1580 c.c.

of hydrogen were absorbed during 65 minutes. The solution was filtered, evaporated, and made alkaline with sodium hydroxide solution, and the base extracted with ether. *7-Amino-1 : 2 : 3 : 4-tetrahydroisoquinoline* (2·35 g.) crystallised from benzene in prisms, m. p. 120—121° (Found: C, 73·1; H, 8·5; N, 18·9. $C_9H_{12}N_2$ requires C, 72·9; H, 8·1; N, 18·9%).

7-Amino-2-benzoyl-1 : 2 : 3 : 4-tetrahydroisoquinoline.—2-Benzoyltetrahydro-7-nitroisoquinoline (4·3 g.) in ethanol (100 c.c.) was shaken with hydrogen in the presence of Raney nickel (2 g.). 1070 c.c. of hydrogen were absorbed during 3 hours. The *base* (3·8 g.) crystallised from light petroleum (b. p. 60—80°) in cream-coloured plates, m. p. 129° (Found: N, 11·4. $C_{16}H_{16}ON_2$ requires N, 11·1%).

7-Amino-2-benzyl-1 : 2 : 3 : 4-tetrahydroisoquinoline.—(*a*) 7-Amino-2-benzoyltetrahydroisoquinoline (1 g.) was added to a solution of lithium aluminium hydride (500 mg.) in dry ether (100 c.c.) and refluxed overnight. The mixture was decomposed by addition of 2N-sodium hydroxide, and the ethereal solution separated and dried (K_2CO_3). The residue (900 mg.) remaining after evaporation of the ether crystallised from light petroleum (b. p. 80—100°) in long yellow needles, m. p. 86—87° alone or on admixture with the material synthesised as in (*b*) below.

(*b*) *2-Benzyl-1 : 2 : 3 : 4-tetrahydro-7-nitroisoquinoline.* 2-2′-Chloroethyl-5-nitrobenzyl chloride (Mann and Beeby, *loc. cit.*) (2·5 g.) was refluxed in ethanol (25 c.c.) with benzylamine (3·5 g.) for 1 hour. The mixture was poured into water and extracted with ether. The extract was dried (K_2CO_3) and the *hydrochloride* (3 g.) precipitated by dry hydrogen chloride. It crystallised from ethanol in prisms, m. p. ~248° (softens at 234°) (Found: N, 9·6. $C_{16}H_{16}O_2N_2$,HCl requires N, 9·2%).

7-Amino-2-benzyl-1 : 2 : 3 : 4-tetrahydroisoquinoline.—2-Benzyltetrahydro-7-nitroisoquinoline (1 g.) in ethanol (10 c.c.) was shaken with hydrogen in the presence of Raney nickel (1 g.). 225 c.c. of hydrogen were absorbed during 10 hours. The *product* (500 mg.) crystallised from light petroleum (b. p. 60—80°) in cream-coloured plates, m. p. 88° (Found: C, 80·6; H, 7·6; N, 11·8. $C_{16}H_{18}N_2$ requires C, 80·7; H, 7·6; N, 11·8%).

2-Benzyl-1 : 2 : 3 : 4-tetrahydroisoquinoline.—*iso*Quinoline (5 g.) and benzyl chloride (5 g.) were refluxed in ethanol (10 c.c.) for 6 hours. The product was precipitated by addition of dry ether, dried, and dissolved in a minimum of water, and excess of potassium iodide added. *2-Benzylisoquinolinium iodide* (14 g.) was filtered off and crystallised from methanol; it formed yellow prisms, m. p. 178° (Found: N, 4·0. $C_{16}H_{14}NI$ requires N, 4·0%). This product (10 g.) was suspended in methanol (100 c.c.) and shaken with hydrogen in the presence of platinum oxide (300 mg.), and the whole filtered. 1400 c.c. of hydrogen were absorbed during 6 hours. The base (6·2 g.) was isolated and distilled, having b. p. 200—205° (bath-temp.)/20 mm. The *hydrochloride* crystallised from ethanol in plates, m. p. 204° (Found: N, 5·5. $C_{16}H_{17}N$, HCl requires N, 5·4%). Nitration of the base, as described for tetrahydroisoquinoline, gave the 2-benzyl-1 : 2 : 3 : 4-tetrahydro-7-nitroisoquinoline hydrochloride, m. p. 248° (softens at 234°) described in (*b*) above (Found: N, 9·6%).

2-n-Butyl-1 : 2 : 3 : 4-tetrahydro-7-nitroisoquinoline.—*n*-Butyltetrahydroisoquinoline (12 g.) in sulphuric acid (*d* 1·84; 60 c.c.) was added to potassium nitrate (12 g.) in sulphuric acid (*d* 1·84; 60 c.c.) with ice cooling. The product was isolated as described for tetrahydro-7-nitroisoquinoline. The hydrochloride crystallised from ethanol in prisms, m. p. 234—235° (rapid heating; with slow heating, m. p. ~225°) (Found: C, 57·7; H, 7·2; N, 10·6. Calc. for $C_{13}H_{19}O_2N$,HCl: C, 57·8; H, 7·3; N, 10·5%). There was no depression in m. p. observed with a sample kindly supplied by Dr. Mann (cf. Mann and Beeby, *loc. cit.*, who cite m. p. 224—226°).

Ultra-violet absorption spectra.—These were measured in ethanol using a Hilger "Uvispek" photoelectric spectrophotometer; cell path 1 cm.

Since ethanolic solutions of both 7- and 5-aminoisoquinolines exhibit an intense blue fluorescence—a property associated with deviation from Beer's law (cf. *inter al.*, Braude, Fawcett, and Timmons, *J.*, 1950, 1019)—comparisons of the ultra-violet absorption spectra of the two samples of 7-aminoisoquinolines were made at the same molar concentrations. For this reason also no comparison has been attempted with the data presented by Ewing and Steck (*J. Amer. Chem. Soc.*, 1948, **70**, 3397) for 1-, 4-, and 5-aminoisoquinoline. Results were: Our sample ($10·25 \times 10^{-5}$ moles/l.), $\lambda_{max.}$ 238, 284, and 361 mμ. (log. $\epsilon_{max.}$ 4·55, 3·98, and 3·41, respectively). Dr. Manske's sample ($10·1 \times 10^{-5}$ moles/l.), $\lambda_{max.}$ 238, 284, and 361 mμ. (log. $\epsilon_{max.}$ 4·56, 3·98, and 3·42, respectively).

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THE SCHOOL OF PHARMACY,
17, BLOOMSBURY SQUARE, W.C.1.
DEPT. OF BIOCHEMISTRY, INSTITUTE OF PSYCHIATRY,
MAUDSLEY HOSPITAL, DENMARK HILL, S.E.5.

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634. *Anodic Syntheses. Part V.* Electrolysis of N-Acylamino-acids. A Novel Alkoxylation Reaction.*

By R. P. Linstead, B. R. Shephard, and B. C. L. Weedon.

Electrolysis of *N*-acyl-glycines and -DL-α-alanines in methanol gives *N*-methoxymethyl- and *N*-1′-methoxyethyl-amides respectively in good yields. Analogous reactions occur in both ethanol and *iso*propanol.

Under similar conditions *N*-acyl derivatives of 6-aminohexanoic acid, γ-aminobutyric acid, and β-alanine undergo the normal Kolbe reaction giving the corresponding derivatives of polymethylenediamines in *ca.* 20—40% yields.

The Kolbe synthesis of compounds of the type R·R by electrolysis of the acids $R·CO_2H$ is known to be accompanied by side reactions, a number of which were described by Kolbe himself (*Annalen*, 1849, **69**, 257). The extent to which by-products are formed is governed both by the experimental conditions and, to a marked degree, by the structure of the acid electrolysed. A survey of the literature reveals that presence of substituents α to the carboxyl group has the most pronounced influence, as would be expected, and may result in the Kolbe coupling reaction being largely or completely suppressed. Thus although normal coupling occurs with alkyl hydrogen malonates (Brown and Walker, *ibid.*, 1891, **261**, 107; Hickling and Westwood, *J.*, 1938, 1039) and, to a smaller extent, with α-phenyl- (Fichter and Stenzl, *Helv. Chim. Acta*, 1939, **22**, 970) and α-aryloxy-acetic acids (*idem*, *loc. cit.*; Fichter and Kestenholz, *ibid.*, 1942, **25**, 785), and a few α-alkyl-acids, little or no coupling has been reported for most α-alkyl-acids, for α-methoxy-, α-hydroxy-, α-halogeno-, α-keto-, α-cyano-, and α-amino-acids (for a review see Brockman, " Electro-Organic Chemistry," New York, 1926) or for di- or tri-phenylacetic acid (van der Hoek and Nauta, *Rec. Trav. chim.*, 1942, **61**, 845; Riccoboni, *Gazzetta*, 1940, **70**, 748). However as the experimental conditions employed in much of the early work in this field cannot now be regarded as the most suitable for coupling, further study seemed desirable. Moreover an investigation of the competing reactions might well reveal new and valuable synthetic processes. With these considerations in mind an exploratory investigation of the electrolysis of a number of substituted acids has been put in hand. The results with *N*-acylamino-acids are reported in the present communication.

Fichter and Schmidt (*Helv. Chim. Acta*, 1920, **3**, 704) demonstrated that electrolysis, in aqueous solutions, of α-amino-acids or their *N*-acyl or *N*-sulphonyl derivatives led to complete disruption of the molecule and not to coupling of the Kolbe type. In the application of the Kolbe reaction to fatty acids the use of methanolic rather than aqueous solutions has frequently been found advantageous, and the present work has been confined to non-aqueous solutions. These have yielded results quite different from those reported by Fichter.

Electrolysis of *N*-benzoylglycine in methanol furnished in good yield (61%) a neutral product which, on the basis of the analytical results and the formation of bisbenzamidomethane (II) and formaldehyde on treatment with mineral acid, is formulated as *N*-methoxymethyl-benzamide (I; R = Ph). This structure was confirmed by treatment of *N*-hydroxymethyl-benzamide with methanolic hydrogen chloride (cf. U.S.P. 2,364,737; B.P. 557,932), which gave in 30% yield a product identical with that prepared anodically.

$$R·CO·NH·CH_2·CO_2H \longrightarrow R·CO·NH·CH_2·OMe \quad (I) \qquad (Ph·CO·NH)_2CH_2 \quad (II)$$

$$R·CO·NH·CHMe·CO_2H \longrightarrow R·CO·NH·CHMe·OMe \quad (III)$$

Anodic methoxylation also took place readily with *N*-acetyl- and *N*-carbobenzyloxy-glycine, giving *N*-methoxymethyl-acetamide (I; R = Me) and -benzylurethane (I; R = $Ph·CH_2·O$) in 78 and 74% yield respectively. Similarly *N*-acetyl- and N-benzoyl-DL-α-alanine gave the *N*-1′-methoxyethyl-amides (III; R = Me and Ph) in 85 and 91% yield respectively.

The use of solvents other than methanol was also briefly investigated, and by electrolysis of *N*-benzoylglycine in ethanol and *iso*propanol, and of *N*-benzoyl-DL-α-alanine in ethanol, the corresponding ethoxy- and *iso*propoxy-alkylamides were obtained (56—70%).

* Part IV, *J.*, 1951, 1130.

These reactions can be generalised as follows:

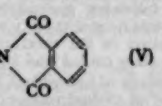
$$X\cdot NH\cdot CHR\cdot CO_2H + R'\cdot OH \longrightarrow X\cdot NH\cdot CHR\cdot OR' + CO_2$$

where X is acyl, R hydrogen or methyl, and R' alkyl. The alkoxyalkyl-amides (acylamino-ethers) so produced are of a rare type hard to prepare in other ways. The yields are high and the products easily obtained as crystalline solids or colourless distillable liquids.

Electrolysis of *N*-phenylacetylglycine in acetic acid solution yielded *N*-(acetoxymethyl)-phenylacetamide (IV) (38%), previously prepared by the action of lead tetra-acetate on *N*-phenylacetylglycine (Süs, *Annalen*, 1949, **564**, 137).

From a few of the electrolyses in alcohols described above, small amounts (<15%) of α-diamine derivatives, the products of normal coupling, were also isolated.

$Ph\cdot CH_2\cdot CO\cdot NH\cdot CH_2\cdot OAc$ (IV)



(V)

When *N*-methoxymethylbenzamide (I; R = Ph) and the corresponding ethoxy- and *iso*propoxy-compounds were heated with phthalimide, *N*-phthalimidomethylbenzamide (V) was obtained. A number of the other 1-alkoxyalkyl derivatives described above were also shown to react similarly with phthalimide and were conveniently characterised in this way.

The only previous well-authenticated example of anodic alkoxylation was reported by van der Hoek and Nauta (*loc. cit.*) who isolated methoxydiphenylmethane (35% yield) from the products formed by electrolysis of diphenylacetic acid in a mixture of methanol and pyridine. Anodic alkoxylations, in general, are reminiscent of the formation of alcohols on electrolysis of fatty acids in aqueous solution (Hofer and Moest, *Annalen*, 1902, **323**, 284). The Hofer–Moest reaction is promoted by various inorganic anions and can involve attack at positions both α and β to the eliminated carboxyl group (Kruis and Schanzer, *Z. physikal. Chem.*, 1942, **191**, *A*, 301). In the present work, however, no evidence was obtained of β-attack on derivatives of DL-α-alanine.

Several plausible mechanisms could be put forward to account for these anodic alkoxylations but it is not proposed to speculate on these at present. Experiments designed to provide information on this aspect are in hand. It is hoped to determine also the structural features which favour alkoxylation and related reactions.

After the study of derivatives of α-amino-acids, attention was directed to acids with the amino- and carboxyl groups separated from one another. Fichter and Schmidt (*loc. cit.*) were unable to detect the normal Kolbe reaction on electrolysis of β-alanine or its *N*-benzoyl derivative in aqueous solution, but, more recently, Offe (*Z. Naturforsch*, 1947, **2b**, 182, 185) has stated that electrolysis in methanol of *N*-acyl or *N*-alkylsulphonyl derivatives of amino-acids other than those of the α-series leads to the corresponding derivatives of diamines by normal coupling. This conclusion was based on the results of electrolysing γ-phthalimido-butyric acid and derivatives of 6-aminohexanoic acid but yields were given in one case only. We find that normal Kolbe coupling occurs in the electrolysis in methanol of a considerable range of acylamino-acids other than those of the α-series. The reaction

$$X\cdot NH\cdot[CH_2]_n\cdot CO_2H \longrightarrow X\cdot NH\cdot[CH_2]_{2n}\cdot NH\cdot X$$

proceeds in about 30% yield where *n* is 2, 4, or 6. Thus 6-acetamido-, 6-benzamido-, and 6-carbobenzyloxyamino-hexanoic acids yielded the corresponding derivatives of 1 : 10-diamino-decane (31, 23, and 38% severally). 1 : 6-Biscarbobenzyloxyaminohexane was similarly prepared (35%) from γ-carbobenzyloxyaminobutyric acid. Electrolysis of *N*-benzoyl- and *N*-carbobenzyloxy-β-alanine furnished the derivatives of 1 : 4-diaminobutane in 20 and 33% yield. From *N*-benzoyl-β-alanine a small amount of 2-phenyloxazoline was isolated (in the form of its picrate) as by-product. In general, however, the nature of the side products in these reactions remains to be determined.

Experimental.

Apparatus.—Two cells, "A" and "B," were employed. These consisted of cylindrical glass vessels containing two parallel platinum plates, placed 1—2 mm. apart, as electrodes. In cell "A" the electrodes measured 4 × 2·5 cm., and in cell "B" 2·5 × 2·5 cm.

Electrolyses in Alcohols.—Technical absolute alcohols were used as solvents.

The acylamino-acid was dissolved in the alcohol to which sufficient sodium had previously been added to neutralise *ca.* 2% of the acid (except in the one experiment using *iso*propanol as solvent, in

which the ammonium salt was electrolysed). While the cell was cooled in an ice-bath, a current (*ca.* 0·1—0·2-amp./sq. cm. anode current density) was passed until the electrolyte became slightly alkaline. This process usually required *ca.* 3—6 times longer than the time calculated on the basis of the current and the amount of acid employed. At the end of the electrolyses, the cell contents were neutralised by the addition of a few drops of acetic acid and the products were isolated as described below.

N-*Methoxymethylbenzamide* (I; R = Ph).—(a) *Anodic synthesis.* *N*-Benzoylglycine (35·8 g.) in methanol (300 c.c.) was electrolysed in cell "A." After neutralisation of the cell contents the solvent was removed under reduced pressure and the residue crystallised from 1 : 5 light petroleum (b. p. 40—60°)–benzene and then from ether, giving N-*methoxymethylbenzamide* (20·0 g.) as prisms, m. p. 72·5° (Found: C, 65·7; H, 6·8; N, 8·3; OMe, 19·1. $C_9H_{11}O_2N$ requires C, 65·4; H, 6·7; N, 8·5; OMe, 18·8%). This, when heated with phthalimide, gave, in 70% yield, *N-phthalimidomethylbenzamide* (V), which crystallised from alcohol in needles, m. p. 184° (Found: C, 68·6; H, 4·4; N, 9·7. $C_{16}H_{12}O_3N_2$ requires C, 68·5; H, 4·3; N, 10·0%). This and the subsequent reactions with phthalimide were carried out by the following general method: The *N*-1′-alkoxyalkyl-amide and an equimolar quantity of phthalimide was heated rapidly to 180—220°, whereupon reaction commenced with evolution of vapours. The temperature of the mixture was raised during 5 minutes to 250°, evolution then ceasing. The mixture was then cooled and the resulting crude *N*-1′-phthalimidoalkyl-amide crystallised.

(b) A solution of anhydrous hydrogen chloride in methanol (1·37N.; 2·0 c.c.) was added to a warm (45°) solution of *N*-hydroxymethylbenzamide (18·0 g.) in anhydrous methanol (20 c.c.; dried over magnesium methoxide). The mixture was kept at 45—50° for ½ hour and then cooled to *ca.* −10° in ice-salt. The solid (12·5 g.), m. p. 40—60°, which separated was removed and extracted with water (100 c.c.) at 30°. The residue (8·1 g.), m. p. 69—70°, was recrystallised from 1 : 4 light petroleum (b. p. 40—60°)–ether and yielded *N*-methoxymethylbenzamide (6·0 g.) as prisms, m. p. 72° undepressed on admixture with a specimen from (a). The phthalimido-derivative had m. p. 184° undepressed on admixture with a specimen from (a).

Bisbenzamidomethane (II).—A mixture of *N*-methoxymethylbenzamide (1·0 g.) and hydrochloric acid (15% w/v; 20 c.c.) was heated rapidly (1 minute) to the b. p. Formaldehyde (identified as its 2 : 4-dinitrophenylhydrazone) was evolved, and on cooling of the acid solution a solid was deposited. This crystallised from ethanol, giving bisbenzamidomethane (0·6 g., 85%) m. p. 218° undepressed on admixture with an authentic specimen (Einhorn, *Annalen*, 1905, **343**, 226, gives m. p. 218°).

N-*Methoxymethylacetamide* (I; R = Me).—Acetylglycine (59 g.) in methanol (500 c.c.) was electrolysed in cell "A." Neutralisation and distillation of the cell contents gave the *amide* (40 g.) as a mobile oil, b. p. 90°/14 mm., n_D^{25} 1·4381, which was miscible with water (Found: C, 46·6; H, 9·0; N, 13·3. $C_4H_9O_2N$ requires C, 46·6; H, 8·8; N, 13·6%). The *phthalimido*-derivative, prepared in 46% yield, crystallised from alcohol in needles, m. p. 184° (Found: C, 60·3; H, 4·6; N, 12·6. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6; N, 12·8%).

Benzyl N-*Methoxymethylurethane* (I; R = Ph·CH_2·O) *and* 1 : 2-*Biscarbobenzyloxyaminoethane.*—*N*-Carbobenzyloxyglycine (10·5 g.) in methanol (20 c.c.) was electrolysed in cell "B." The cell contents were neutralised, the solvent was removed under reduced pressure, and the residue dissolved in light petroleum (b. p. 40—60°; 10 c.c.) containing a few drops of ethyl acetate. A solid (0·5 g.), m. p. 160°, separated and was recrystallised from the same solvent. This yielded 1 : 2-*biscarbobenzyloxyaminoethane*, m. p. 166·5° undepressed on admixture with a specimen prepared from benzyl chloroformate and ethylenediamine (Found: N, 8·5. $C_{18}H_{20}O_4N_2$ require N, 8·5%).

The mother-liquors were evaporated and the residue was distilled, giving *benzyl* N-*methoxymethylurethane* (6·0 g.), b. p. 70° (bath-temp.)/10^{-3} mm., n_D^{20} 1·5162 (Found: C, 61·7; H, 7·0; N, 6·9; OMe, 16·3. $C_{10}H_{13}O_3N$ requires C, 61·5; H, 6·7; N, 7·2; OMe, 15·9%). The *phthalimido*-derivative, prepared in 95% yield, crystallised from alcohol in needles, m. p. 121° (Found: C, 65·7; H, 4·5; N, 9·1. $C_{17}H_{14}O_4N_2$ requires C, 65·8; H, 4·5; N, 9·0%).

N-1′-*Methoxyethylacetamide* (III; R = Me).—Acetyl-DL-α-analine (13·1 g.) in methanol (60 c.c.) was electrolysed in cell "B." Neutralisation and distillation of the cell contents gave the *amide* (10·0 g.) as a water miscible oil, b. p. 71—73°/0·7 mm., n_D^{25} 1·4338 (Found: C, 51·3; H, 9·5; N, 12·2; OMe, 26·0. $C_5H_{11}O_2N$ requires C, 51·25; H, 9·5; N, 12·0; OMe, 26·5%).

N-1′-*Methoxyethylbenzamide* (III; R = Ph).—Benzoyl-DL-α-alanine (58 g.) in methanol (300 c.c.) was electrolysed in cell "A." The cell contents were neutralised, concentrated to *ca.* 75 c.c., and cooled. The solid (45 g.), m. p. 85°, which separated was removed. Evaporation of the mother-liquors and distillation of the residue gave a further quantity (7 g.) of product, b. p. 80° (bath-temp.)/10^{-4} mm., m. p. 80°. The crude products were combined and crystallised from ether, giving the *amide* (48 g.) as needles, m. p. 88·5° (Found: C, 66·9; H, 7·5; N, 7·7; OMe, 17·0. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3; N, 7·8; OMe, 17·3%). The *phthalimido*-derivative, prepared in 60% yield, crystallised from alcohol in needles, m. p. 199° (Found: C, 69·3; H, 4·9; N, 9·6. $C_{17}H_{14}O_3N_2$ requires C, 69·4; H, 4·8; N, 9·5%).

1 : 1-*Bisbenzamidoethane.*—A mixture of *N*-1′-methoxyethylbenzamide (5·0 g.) and 2N-hydrochloric acid (20 c.c.) was warmed rapidly (1 minute) to 80°. Acetaldehyde (identified as its 2 : 4-dinitrophenylhydrazone) was evolved, and on cooling of the acid solution a solid was deposited. This was crystallised from alcohol, giving 1 : 1-bisbenzamidoethane (3·0 g., 80%) as needles, m. p. 214° (Found: C, 71·3; H, 5·8; N, 10·3. Calc. for $C_{16}H_{16}O_2N_2$: C, 71·6; H, 6·0; N, 10·4%) (Kraut and Schwartz, *Annalen*, 1884, **223**, 40, give m. p. 202—204°).

N-*Ethoxymethylbenzamide and* 1 : 2-*Bisbenzamidoethane.*—*N*-Benzoylglycine (35·8 g.) in ethanol (300 c.c.) was electrolysed in cell "A." The cell contents were neutralised, filtered (charcoal), concentrated to *ca.* 100 c.c., and cooled, whereupon a solid (4·0 g.), m. p. 225—230°, separated. This was crystallised from glacial acetic acid, giving the diamide as needles, m. p. 244°, undepressed on admixture with an authentic specimen (Ladenburg, *Ber.*, 1895, 28, 3068, gives m. p. 244°).

The alcoholic mother-liquors were evaporated and the residue distilled, giving *N-ethoxymethylbenzamide* (20·0 g., 56%) as a viscous oil, b. p. 70—80° (bath-temp.)/10^{-3} mm., which slowly solidified. Low-temperature crystallisation from ether gave needles, m. p. 40° (Found: C, 67·2; H, 7·4; N, 7·8; OEt, 25·3. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3; N, 7·8; OEt, 25·1%). The phthalimido-derivative, prepared in 63% yield, had m. p. 186°, undepressed on admixture with the specimen prepared from *N*-methoxymethylbenzamide.

N-iso*Propoxymethylbenzamide and* 1 : 2-*Bisbenzamidoethane*.—A solution of *N*-benzoylglycine (3·58 g.) and the ammonium salt of *N*-benzoylglycine (from 3·58 g. of the acid) in *iso*propanol (100 c.c.) was electrolysed in cell "A." During the electrolysis a solution of *N*-benzoylglycine (28·6 g.) in *iso*propanol (200 c.c.) was added slowly (25 c.c./hour). The cell contents were neutralised and concentrated to 100 c.c., and then ether (100 c.c.) was added. The precipitated crude diamide (2·2 g.), m. p. 238°, was filtered off and the filtrate evaporated. Distillation of the residue gave N-iso*propoxymethylbenzamide* (27·5 g., 70%) as a viscous oil, b. p. 120° (bath-temp.)/5 × 10^{-3} mm., which slowly solidified and had f. p. 15° (Found: C, 68·6; H, 7·6; N, 7·6. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8; N, 7·3%). The phthalimido-derivative, prepared in 30% yield, had m. p. 185° undepressed on admixture with a specimen prepared from *N*-methoxymethylbenzamide.

N-1′-*Ethoxyethylbenzamide*.—Benzoyl-DL-α-alanine (6·6 g.) in ethanol (20 c.c.) was electrolysed in cell "B." Neutralisation and distillation of the cell contents gave the *amide* (5 g., 76%) as a viscous oil, b. p. 70—80° (bath-temp.)/10^{-4} mm., which slowly solidified. Crystallisation from ether at low temperature gave needles, m. p. 61·6° (Found: C, 68·7; H, 8·0; N, 7·5; OEt, 23·4. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8; N, 7·3; OEt, 23·3%).

N-(*Acetoxymethyl*)*phenylacetamide* (IV).—A solution of *N*-phenylacetylglycine (9·0 g.) and anhydrous sodium acetate (1·8 g.) in glacial acetic acid (60 g.) was electrolysed for 1 hour in cell "A," a current of 2·0 amps. being used. The cell contents were then evaporated under reduced pressure, the residue was dissolved in ether, and the solution washed with saturated aqueous sodium carbonate solution. On acidification of the aqueous extract, *N*-phenylacetylglycine (3·0 g.), m. p. 142°, was recovered. The ethereal solution was dried and evaporated. The residue on crystallisation from carbon tetrachloride and finally from alcohol gave *N*-(acetoxymethyl)phenylacetamide as needles (2·4 g.), m. p. 97·5° (Süs, *Annalen*, 1949, **564**, 137, give m. p. 98—99°) (Found: C, 64·1; H, 6·5; N, 6·9. Calc. for $C_{11}H_{13}O_3N$: C, 63·8; H, 6·3; N, 6·8%).

Bisphenylacetamidomethane.—A suspension of the preceding acetoxy-compound (2·1 g.) in hydrochloric acid (15% w/v; 20 c.c.) was gently boiled for 5 minutes. When the resulting solution was cooled, a solid separated. This on crystallisation from alcohol gave bisphenylacetamidomethane (0·5 g.), m. p. 209° (*idem*, *loc. cit.*, give m. p. 209—210°).

1 : 10-*Diacetamidodecane*.—6-Acetamidohexanoic acid (8·7 g.) in methanol (30 c.c.) was electrolysed in cell "B." The cell contents were neutralised, the solvent was evaporated, and the residue was crystallised (charcoal) from water, giving 1 : 10-diacetamidodecane (2·0 g.) as needles, m. p. 130° (Offe, *Z. Naturforsch*, 1947, **2** b, 185, gives m. p. 131° and 25—40% yield).

1 : 10-*Bisbenzamidodecane*.—6-Benzamidohexanoic acid (11·8 g.) in methanol (40 c.c.) was electrolysed in cell "B." The hot cell contents were neutralised, filtered (charcoal), and concentrated to 15 c.c., whereupon a solid (2·2 g.), m. p. 145°, separated. This was crystallised from 1 : 1 chloroform–ethyl acetate, giving 1 : 10-bisbenzamidodecane as needles, m. p. 152° (Found: C, 75·5; H, 8·5; N, 7·5. Calc. for $C_{24}H_{32}O_2N_2$: C, 75·7; H, 8·5; N, 7·4%) (*idem*, *loc. cit.*, gives m. p. 153°).

1 : 10-*Biscarbobenzyloxyaminodecane*.—6-Carbobenzyloxyaminohexanoic acid (13·3 g.), prepared in 80% yield from 6-aminohexanoic acid, had m. p. 55°. It was electrolysed in methanol (50 c.c.) in cell "B." The cell contents were extracted with boiling methanol, the extract was neutralised and filtered, and the filtrate concentrated to 20 c.c. Ether (100 c.c.) was added and the precipitated solid (4·2 g.), m. p. 115—120°, was crystallised from alcohol, giving 1 : 10-*biscarbobenzyloxyaminodecane* as needles, m. p. 123° (Found: C, 70·6; H, 8·3; N, 6·7. $C_{38}H_{44}O_6N_2$ requires C, 70·9; H, 8·2; N, 6·4%).

1 : 6-*Biscarbobenzyloxyaminohexane*.—γ-Carbobenzyloxyaminobutyric acid (11·0 g.), prepared in 68% yield from γ-aminobutyric acid, had m. p. 64·5°. It was electrolysed in methanol (100 c.c.) in cell "A." The hot cell contents were neutralised, filtered, and concentrated to 20 c.c., and ether (100 c.c.) was added. The solid (3·5 g.), m. p. 120°, which separated was crystallised from benzene giving 1 : 6-*biscarbobenzyloxyaminohexane* as needles, m. p. 126° (Found: C, 68·4; H, 7·3; N, 7·5. $C_{22}H_{28}O_4N_4$ requires C, 68·7; H, 7·4; N, 7·3%).

1 : 4-*Bisbenzamidobutane and* 2-*Phenyloxazoline*.—*N*-Benzoyl-β-alanine (17·4 g.) in methanol (55 c.c.) was electrolysed in cell "A," and the cell contents were then neutralised. The solvent was removed under reduced pressure, the residue dissolved in chloroform, and the solution washed with aqueous sodium carbonate, dried, and concentrated to 20 c.c. A solid (2·6 g.), m. p. 170°, which separated was crystallised from alcohol, giving 1 : 4-bisbenzamidobutane as needles, m. p. 176° undepressed on admixture with an authentic specimen (von Udránszky and Baumann, *Z. physiol. Chem.*, 1889, **13**, 174, give m. p. 175—176°).

The chloroform mother-liquors were evaporated. Distillation of the residue, which was accompanied by extensive decomposition, gave a heterogeneous oil (1·0 g.), b. p. 70°/3 × 10^{-3} mm. (Found: OMe, 7·6%). Treatment with an alcoholic solution of picric acid and crystallisation of the product from alcohol gave needles, m. p. 176—177° undepressed on admixture with the picrate of 2-phenyloxazoline (Gabriel and Heymann, *Ber.*, 1890, **23**, 2493, give m. p. 177°) (Found: N, 14·8. Calc. for $C_{15}H_{14}O_8N_4$: N, 14·9%).

1 : 4-*Biscarbobenzyloxyaminobutane*.—Carbobenzyloxy-β-alanine (15·6 g.) in methanol (50 c.c.) was electrolysed in cell "B." The cell contents were neutralised, diluted with chloroform, and filtered

(charcoal). The filtrate was concentrated to *ca.* 30 c.c., ether (50 c.c.) was added, and the precipitated solid (4·1 g.), m. p. 140°, separated. Crystallisation from cellosolve gave 1 : 4-*biscarbobenzyloxyaminobutane*, m. p. 150·5° (Found : C, 67·1; H, 6·9; N, 8·0. $C_{28}H_{24}O_4N_2$ requires C, 67·4; H, 6·8; N, 7·9%).

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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635. *The Crystal Structure of Potassium Hydrogen Bisphenylacetate.*

By MANSEL DAVIES and W. J. ORVILLE THOMAS.

The infra-red absorption spectra of solid phenylacetic acid, potassium phenylacetate, and potassium hydrogen bisphenylacetate have been recorded between 650 and 3500 cm.$^{-1}$. These spectra do not support the suggestion that a symmetrical hydrogen bridge occurs in the acid salt. The latter shows C–O frequencies which establish the presence in it of more or less normal carboxylic acid and carboxylate ion groups.

A RECENT *X*-ray investigation of the crystal structure of potassium hydrogen bisphenylacetate, $KH(O_2C{\cdot}CH_2Ph)_2$ (Speakman, *J.*, 1949, 3357), has indicated that the structure consists of infinite layers of potassium ions and hydrogen atoms (or ions) situated between layers of phenylacetate residues, the carboxyl group of the residues being linked together from either side by the potassium ions and hydrogen atoms (or ions). Each hydrogen is situated between two oxygen atoms, thus forming a short hydrogen bridge.

Other *X*-ray studies of carboxylic acids in the crystalline form (Robertson and Woodward, *J.*, 1936, 1817; Brill, Hermann, and Peters, *Ann. Physik*, 1942, **42**, 357; Dunitz and Robertson, *J.*, 1947, 142) indicated that the proton is nearer one of the oxygen atoms joined by a hydrogen bond than to the other; *i.e.*, the hydrogen is unsymmetrically placed. In potassium hydrogen bisphenylacetate it is reported that the hydrogen bridge is crystallographically symmetrical. This symmetry, it was indicated (*J.*, 1949, 3363), may be either statistical or the result of the hydrogen actually lying at the mid-point. The latter structure was thought to be possible as a resonance hybrid involving a number of valence-bond configurations. If this symmetrical H-location were correct a number of interesting points would emerge : in particular the covalent hydroxyl and carbonyl bonds which normally exist in the carboxylic acids would be considerably modified. It is to be expected then that, in the infra-red spectrum of the acid salt, the corresponding valence vibration frequencies would be displaced from their "normal" values. In order to verify these points the infra-red spectrum of potassium hydrogen bisphenylacetate has been studied. As an aid in the interpretation of the spectrum the spectra of phenylacetic acid and potassium phenylacetate were also recorded.

EXPERIMENTAL.

Materials.—Potassium hydrogen bisphenylacetate was prepared (Smith and Speakman, *Trans. Faraday Soc.*, 1948, **44**, 1031) by dissolving an equivalent of the acid and half an equivalent of

(P = $CH_2Ph{\cdot}CO_2$).	Absorption frequencies in cm.$^{-1}$.						
HP	3058 s	—	2710 m	2618 m	—	1710 s	—
KP	3049 s	2915 s	—	—	—	—	1600 s
KHP_2	3042 s	2976 s	—	—	1946 w	1755 s	1570 s
Assignment	—	—	—	—	—	ν(C=O)	ν_a(C=O)
HP	1505 m	1458 m	1410 s	1295 s	1237 m	1195 m	1155 m
KP	1500 m	1460 m	1410 s	1290 s	—	1190 m	1158 s
KHP_2	1500 m	1460 m	1375 s	1290 s	1245 s	1206 m	1155 s
Assignment	R	R	δ(OH) or ν_s(C=O)	R	ν(C—O)	R	R
HP	1074 m	1030 m	985 w	965 m	—	927 s	906 s
KP	1073 s	1032 s	985 w	970 w	940 s	930 s	907 m
KHP_2	1073 m	1036 m	985 w	965 w	945 m	925 m	—
Assignment	R	R	R	R	—	R	—
HP	893 s	—	840 m	755 s	—	701 s	680 m
KP	—	855 m	840 m	770 s	735 s	702 s	688 m
KHP_2	890 s	860 s	841 s	763 m	728 m	695 w	—
Assignment	—	—	R	R		R	—

potassium hydroxide in hot alcohol. The acid salt crystallized out on cooling. It was recrystallized from alcohol and kept in a well-stoppered bottle.

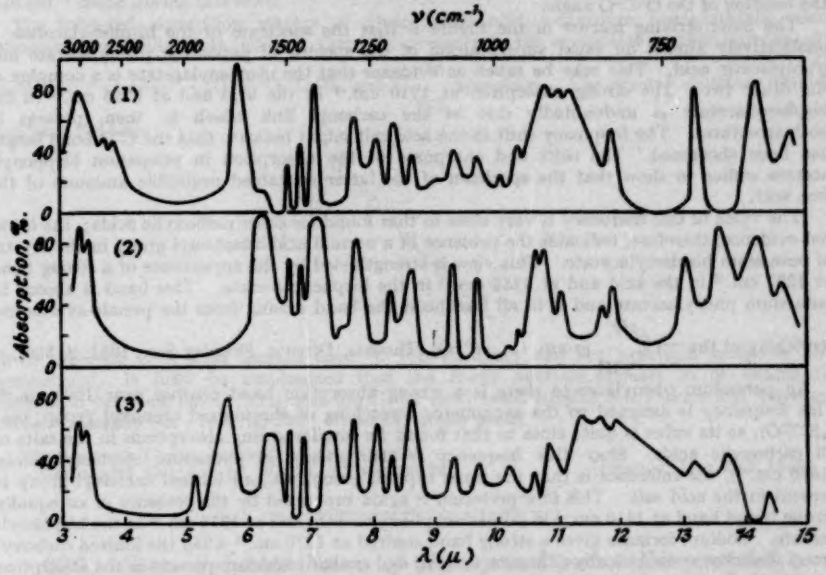
Potassium phenylacetate was prepared by the neutralization of a solution of phenylacetic acid with potassium carbonate. The salt was obtained by crystallization from 2 : 1 water–ethyl alcohol.

Apparatus and Technique.—A Grubb–Parsons S.3 spectrometer with rock-salt prism was used.

The crystalline specimens were melted as thin films between rock-salt plates. In order to check whether any breakdown of the double salt occurred on melting, samples were melted, allowed to resolidify, and remelted; no change in m. p. was detected. Intercomparison of the spectra confirmed that little, if any, decomposition of the acid salt resulted from this treatment.

The results obtained are given in the Table and Figure.

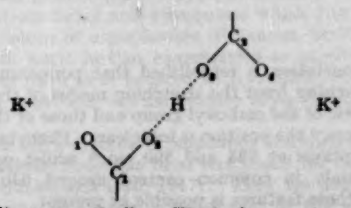
The infra-red absorption spectra of phenylacetic acid (1), *potassium phenylacetate* (2), *and potassium hydrogen bisphenylacetate* (3).



Examination of the Figure and Table shows that a large number of frequencies exists with the same or slightly altered values in the spectra of all the substances. These common frequencies are probably due to vibrations within the $C_6H_5{\cdot}CH_2$ radical, since this is common to all the substances studied. These frequencies are labelled R in the Table. Similar values for these "hydrocarbon" frequencies are found in related structures (Bailey, Hales, Ingold, and Thompson, *J.*, 1936, 931; Angus, Ingold, and Leckie, *J.*, 1936, 925; Davies, *J. Chem. Physics*, 1948, **16**, 267).

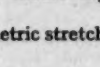
Discussion.

The carboxyl group structure in crystalline potassium bisphenylacetate may be represented as

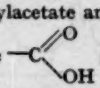


where the bonds are shown diagrammatically. The hydrogen atom (or ion) is situated between two oxygen atoms that are some 2·55—2·65 Å apart (Speakman, *loc. cit.*). If the hydrogen

bridge is symmetrical then the O–H separation will be some 1·30 Å. This may be compared with the normal O–H bond length of 0·97 ± 0·01 Å. The increase in length of some 35% would be expected to modify the O–H bond vibrations considerably.

With a symmetrical hydrogen bridge groups $O_{(1)}C_{(1)}O_{(2)}$ and $O_{(3)}C_{(2)}O_{(4)}$ should have identical electronic structures. Effectively this would mean that only two different C–O bond distances would exist in the crystal structure. The values quoted for these lengths by Speakman, *viz.*, 1·18 and 1·24, each ±0·05 Å, are lower than the values normally quoted for carboxylic acids (*loc. cit.*) and salts (Zachariassen, *J. Amer. Chem. Soc.*, 1940, **61**, 1011). In the spectrum of potassium bisphenylacetate we should expect to find, then, two frequencies only associated with the symmetric and asymmetric stretching of the  group, and one associated with the bending of the O–C–O angle.

The most striking feature in the Figure is that the spectrum of the bisphenylacetate is qualitatively almost an exact superposition of the spectra of potassium phenylacetate and phenylacetic acid. This may be taken as evidence that the bisphenylacetate is a complex of the other two. The strong absorption at 1710 cm.$^{-1}$ in the acid and at 1755 cm.$^{-1}$ in the bisphenylacetate is undoubtedly due to the carbonyl link which is, then, present in both structures. The frequency shift in the acid salt might indicate that the C=O bond length has been shortened. The shift and sharpness of the absorption in potassium bisphenylacetate suffice to show that the specimen of the latter contained negligible amounts of the free acid.

The value of this frequency is very close to that found for other carboxylic acids; the infrared evidence, therefore, indicates the presence of a normal acidic carbonyl group in the crystal of potassium bisphenylacetate. This view is strengthened by the appearance of a strong band at 1237 cm.$^{-1}$ in the acid and at 1245 cm.$^{-1}$ in the bisphenylacetate. This band is absent in potassium phenylacetate and is in all likelihood the band arising from the pseudo-symmetric stretching of the  group, *i.e.*, ν(C–O) (Thomas, *Discuss. Faraday Soc.*, 1951, **9**, 339).

In potassium phenylacetate there is a strong absorption band centred near 1600 cm.$^{-1}$. This frequency is assigned to the asymmetric stretching of the ionized carboxyl group, *viz.*, $\nu_a(C\cdots O)$, as its value is quite close to that found for similar strong absorptions in the salts of all carboxylic acids. Since this frequency is also present in potassium bisphenylacetate (1570 cm.$^{-1}$), the inference is that the same type of group, *viz.*, an ionized carboxyl group is present in the acid salt. This interpretation is again supported by the presence of an equally strong broad band at 1410 cm.$^{-1}$ in potassium phenylacetate and at 1375 cm.$^{-1}$ in the bisphenylacetate. Sodium formate gives a strong band centred at 1370 cm.$^{-1}$ when the ionized carboxyl group stretches symmetrically (Thomas, *loc. cit.*) and similar bands are present in the absorption spectra of all carboxylate salts.

It may be pointed out here that the sharper absorption band which appears at 1410 cm.$^{-1}$ in phenylacetic acid arises from the bending of the O–H links in that crystal. This band decreases markedly in intensity on lowering the concentration of solutions of the acid in carbon tetrachloride. The absorption at 1363 cm.$^{-1}$ in carbon tetrachloride solutions of formic acid behaved similarly and was assigned the same deformation vibration in the associated carboxyl group (Thomas, *loc. cit.*). This band at 1410 cm.$^{-1}$ in phenylacetic acid should thus be absent in the spectra of potassium phenylacetate and bisphenylacetate; the broader bands found in this region for the salts have already been assigned to the symmetrical stretching of the group.

Thus, the important conclusion is established that potassium bisphenylacetate shows in the solid four frequencies arising from the stretching modes of the carboxyl group—*i.e.*, both those which are characteristic of the carboxyl group and those of the carboxylate ion.

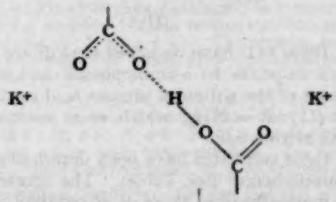
In the region 680—950 cm.$^{-1}$ the position is less clear. Phenylacetic acid and the bisphenylacetate have strong absorptions at 893 and 890 cm.$^{-1}$ whilst potassium phenylacetate and bisphenylacetate have bands in common centred around 940, 850, and 730 cm.$^{-1}$. No convincing explanation of these features is possible at present.

In the high-frequency region the spectrum of phenylacetic acid is appreciably different from that of the bisphenylacetate. The former shows a breadth of absorption typical of

associated carboxyl groups (Davies, *J. Chem. Physics*, 1940, **8**, 577); the latter shows sharp bands which arise from the C–H links (aromatic and aliphatic). It is not clear from the Figure where the O–H vibrational band is centred in potassium bisphenylacetate. A similar apparent disappearance of the O–H stretching frequency has been reported in a number of molecules showing intramolecular interaction (Buswell, Deitz, and Rodebush, *J. Chem. Physics*, 1937, **5**, 501, 726). In these cases where there is certainly no question of a symmetrical hydrogen bridge, it is caused by the overlapping with other (C–H) absorptions of the molecules. This is, of course, the most likely explanation in the present instance.

A band was found at 1946 cm.$^{-1}$ in potassium bisphenylacetate but not detected in phenylacetic acid or potassium phenylacetate. Randall *et al.* ("Infra-red Determination of Organic Structures," D. Van Nostrand Co. Inc., 1949) have, however, reported a band at 1969 cm.$^{-1}$ in phenylacetic acid and presumably this is to be identified with the bisphenylacetate band at 1946 cm.$^{-1}$ found during this work.

The infra-red absorption spectra of phenylacetic acid, potassium phenylacetate, and potassium bisphenylacetate indicate, then, the presence in the crystalline bisphenylacetate of reasonably "normal" C=O, C–O, O–H, and groupings. The crystal structure would then have the form :



Three different C–O bond lengths exist in this structure and the hydrogen bridge is not symmetrical. It may be emphasised that the *X*-ray analysis appears to be unable to distinguish between the C–O(H) and the C⋯O (ion) bond lengths (cf. Davies and Thomas, *Discuss. Faraday Soc.*, 1951, **9**, 335; *Research*, in the press).

The Edward Davies Chemical Laboratories,
University College of Wales, Aberystwyth.

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636. *Some Sulphate Esters of Nitroquinol and 4-Nitrocatechol.*

By J. N. Smith.

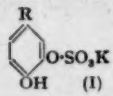
Sulphate esters of nitroquinol (II, III; R = NO_2) and of 4-nitrocatechol (I; R = NO_2) have been prepared by persulphate oxidation of nitrophenols. The absorption spectra of these and of their reduction products have been recorded.

Work in progress in this laboratory on the metabolism of aniline and nitrobenzene required the synthesis of certain sulphate monoesters of dihydroxyanilines. Furthermore, the properties of the sulphate esters of 4-nitrocatechol and nitroquinol which had been prepared in solution in connection with the metabolism of nitrophenols (Robinson, Smith, and Williams, *Biochem. J.*, 1951, **48**, xxvii) seemed to merit further examination as possible enzyme substrates. In the present work, these esters have been isolated as crystalline potassium salts and some of them found to be convenient substrates for the enzyme arylsulphatase (Robinson, Smith, and Williams, unpublished work).

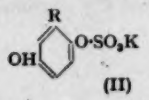
Phenol hydrogen sulphates are well-known compounds and their importance as detoxication products of phenols in the animal body has been recognised for many years (Williams "Detoxication Mechanisms," Chapman and Hall, 1947). They are usually prepared synthetically by the action of sulphur trioxide or chlorosulphonic acid on the phenol in the presence of a tertiary base (*e.g.*, Sobell and Spoerri, *J. Amer. Chem. Soc.*, 1942, **64**, 361; Burkhardt and

Wood, *J.*, 1929, 141). The sulphate esters are also known to be intermediates in the persulphate oxidation of phenols (Elbs, *J. pr. Chem.*, 1893, **48**, 179; Baker and Brown, *J.*, 1948, 2303; Forrest and Petrow, *J.*, 1950, 2340), and the early German patents (D.R.-P. 81,068, 81,297, 81,298; Friedländer, "Fortschritte der Teerfarbenfabrikation," 1894—1897, **4**, 126) claimed the preparation of a number of these compounds by this method though only the preparation of quinol sulphate was described in detail and supported by an analysis. The persulphate oxidation was used in the present work as it offered a convenient means of preparing a monosulphate of a dihydroxyphenol with a free hydroxyl group *para* to the sulphate ester group (cf. Baker and Brown, *loc. cit.*).

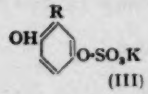
The potassium salts reported here are stable compounds in the dry state and resist hydrolysis by 0·1N-hydrochloric acid at room temperature for 24 hours. In common with other phenol hydrogen sulphates, they are rapidly decomposed by boiling 2N-hydrochloric acid to the corresponding dihydric phenol. The structure of the various compounds follows from this fact and the nature of the starting material (*p*-, *m*-, or *o*-nitrophenol). On reduction with ferrous hydroxide the nitro-compounds yield the corresponding amino-derivatives (I, II; R = NH_2) which slowly become discoloured in air.



(I)



(II)



(III)

Burkhardt and Wood (*J.*, 1929, 141) have observed that dilute nitrous acid readily decomposes *o*-aminophenyl hydrogen sulphate to *o*-aminophenol and sulphuric acid, the solution becoming deep yellow as a result of the action of nitrous acid on the liberated *o*-aminophenol. It has now been found that (II; R = NH_2) which is an *o*-aminohydroxyphenyl hydrogen sulphate behaves similarly with nitrous acid.

The absorption spectra of these sulphates have been determined and compared with those of the relevant nitro- and amino-phenols (see Table). The spectra of the monosulphates (I, II, and III; R = NO_2) differ markedly from those of nitroquinol and 4-nitrocatechol. Nitroquinol in 0·1N-alkali shows a band at 540 mμ. whereas its monosulphates (II and III; R = NO_2) in the same solvent show negligible absorption in this region. 4-Nitrocatechol in alkali shows a peak at 510 mμ. whereas its monosulphate, 2-hydroxy-5-nitrophenyl hydrogen sulphate (I;

	In 0·1N-HCl.					
	$\lambda_{max.}$	$\epsilon \times 10^{-3}$	$\lambda_{max.}$	$\epsilon \times 10^{-3}$	$\lambda_{max.}$	$\epsilon \times 10^{-3}$
p-Nitrophenol	225	6·9	—	—	318	9·8
(I; R = NO_2)	—	—	—	—	315	8·6
4-Nitrocatechol	245	6·3	—	—	345	6·0 ‡
o-Nitrophenol	—	—	280	6·1	352	3·0
(III; R = NO_2)	—	—	273	5·9	360	2·9
2-Nitroquinol	—	—	280	5·5	395	2·8
(II; R = NO_2)	—	—	265	2·6	335	1·8
m-Nitrophenol	225	7·6	275	5·7	320	1·9
p-Aminophenol	—	—	272	1·3	—	—
(I; R = NH_2)	—	—	274	2·0	—	—
m-Aminophenol	—	—	270	1·8	—	—
(II; R = NH_2)	—	—	276	2·0	—	—

	In 0·1N-NaOH.					
	$\lambda_{max.}$	$\epsilon \times 10^{-3}$	$\lambda_{max.}$	$\epsilon \times 10^{-3}$	$\lambda_{max.}$	$\epsilon \times 10^{-3}$
p-Nitrophenol	228	4·5	—	—	402	17·0
(I; R = NO_2)	—	—	—	—	407	18·3
4-Nitrocatechol	—	—	(350	5·8	510	10·3) §
o-Nitrophenol	—	—	282	3·9	412	4·5
(III; R = NO_2)	225	16·8	279	3·9	423	4·8
2-Nitroquinol	238	12·7	—	—	540	3·9
(II; R = NO_2)	235	17·1	—	—	380	1·4
m-Nitrophenol	252	11·2	290	4·2	392	1·58
p-Aminophenol	(234	8·0	303	2·8) *	—	—
(I; R = NH_2)	(230	6·7	298	2·3) †	—	—
m-Aminophenol	—	—	(286	3·2) *	—	—
(II; R = NH_2)	(222	7·4	285	2·7) †	—	—

* In ethanol (Morton and McGookin, *J.*, 1934, 901). † In water.
‡ In ethanol. § In 0·05N-NaOH.

R = NO_2) shows very little absorption in this region, a fact which makes it eminently suitable as a substrate for the assay of arylsulphatase. It is interesting further that the spectra of the isomeric sulphates (II and III; R = NO_2) of nitroquinol also differ from one another. The spectrum of (III; R = NO_2) is very like that of *o*-nitrophenol and it is in fact a sulphated *o*-nitrophenol. Although (II; R = NO_2) is a sulphated *m*-nitrophenol, its spectrum resembles neither that of *m*- nor that of *o*-nitrophenol; a possible explanation is that we have here an instance of steric inhibition of resonance resulting from the presence of the large ·O·SO_3· group *ortho* to the nitro-group, the latter being thus prevented from becoming coplanar with the benzene ring. The spectrum of (I; R = NO_2) is similar to that of *p*-nitrophenol and this substance is in fact a sulphated *p*-nitrophenol. In (I and III; R = NO_2) the nitro- and hydroxyl groups are *para* or *ortho* to each other and the introduction of the ·O·SO_3· groups does not greatly affect the absorption spectrum of the *p*- and *o*-nitrophenols. The spectra of the amino-derivatives (I and II; R = NH_2) correspond to those of *o*- and *m*-aminophenols.

Experimental.

Absorption spectra were measured in a Unicam Spectrophotometer, model SP500. M. p.s are uncorrected.

The nitrophenol (30 g.) was set aside at room temperature for 48 hours in 1 l. of water containing potassium hydroxide (70 g.) and potassium persulphate (70 g.). The dark solution was then acidified to pH 4 with 2N-sulphuric acid, and the free phenol extracted with ether. Neutralisation with potassium carbonate and evaporation of the aqueous solution *in vacuo* at 50—60° left a solid residue which was extracted with cold acetone–water (2 : 1 v/v; 1 l.). The acetone solution was evaporated *in vacuo*, leaving a tarry residue of the sulphate ester which, after crystallisation from a small volume of water, was free from inorganic sulphate and phenol.

Potassium 2-Hydroxy-5-nitrophenyl Sulphate.—The *salt* (I; R = NO_2) (yield, 6 g. from 30 g. of *p*-nitrophenol) crystallised as brown leaflets (decomp. 245—280°), soluble to the extent of about 2% in water at 20° (Found: C, 26·2; H, 1·8; N, 4·3; K, 14·2. $C_6H_4O_7NSK$ requires C, 26·4; H, 1·5; N, 5·1; K, 14·3%). It gave a red colour with ferric chloride. On hydrolysis with 2N-sulphuric acid, followed by ether extraction, it yielded 4-nitrocatechol (m. p. and mixed m. p. 176°) almost quantitatively.

Potassium 4-Hydroxy-3-nitrophenyl Sulphate.—The *salt* (III; R = NO_2) (Found: C, 26·6; H, 1·7; N, 4·7%) (yield, 12 g. from 30 g. of *o*-nitrophenol) crystallised as deep yellow prisms (decomp. 256—257°), showing a solubility of about 2% in water at 20°. A small sample was hydrolysed as above and the liberated phenol examined chromatographically according to the method of Robinson, Smith, and Williams (*Biochem. J.*, in the press) which permits separation of nitroquinol from 3-nitrocatechol. Only nitroquinol was present and in a larger experiment this was isolated in almost quantitative yield (m. p. and mixed m. p. 132°).

Potassium 4-Hydroxy-2-nitrophenyl Sulphate.—The salt (II; R = NO_2) (8 g. from 30 g. of *m*-nitrophenol) crystallised as lemon-yellow prisms of the *monohydrate* which had no sharp decomposition point (Found: C, 24·9; H, 2·4; N, 4·5. $C_6H_4O_7SK,H_2O$ requires C, 24·7; H, 2·1; N, 4·8%). It gave a wine-red colour with ferric chloride and was soluble to about 10% in water at 20°. The phenol liberated on acid hydrolysis was shown by paper chromatography to be free from 3- or 4-nitrocatechol, and 2-nitroquinol was isolated in almost quantitative yield (m. p. and mixed m. p. 132°).

The above compounds were reduced by heating them (1·5 g.) on a water-bath for 40 minutes with crystalline ferrous sulphate (15 g.) and potassium carbonate (9 g.) in water (150 ml.). Filtration and evaporation left residues of the aminophenol sulphates which were extracted with acetone–water (2 : 1 v/v) till all amino-compounds were removed. The extracts were evaporated to dryness and the residues crystallised from a little water or ethanol–water containing a trace of sodium dithionite.

Potassium 5-Amino-2-hydroxyphenyl Sulphate.—The salt (I; R = NH_2) [(0·7 g. from 1·5 g. of (I; R = NO_2)] crystallised as colourless needles of the *monohydrate* (decomp. 205—210°) (Found: C, 27·2; H, 3·2; N, 5·4; K, 15·1. $C_6H_4O_5NSK,H_2O$ requires C, 27·6; H, 3·1; N, 5·4; K, 15·0%), moderately soluble in water and giving a wine-red colour with ferric chloride. It reduced cold neutral silver nitrate, and gave a deep blue colour in the diazo-reaction (nitrous acid, followed by ammonium sulphamate and dimethyl-α-naphthylamine).

Potassium 2-Amino-4-hydroxyphenyl Sulphate.—The *salt* (II; R = NH_2) [(1·5 g. from 2 g. of (II; R = NO_2)] crystallised as colourless prisms which darkened when kept and were moderately soluble in water (Found: C, 29·7; H, 3·0; N, 5·6. $C_6H_6O_5NSK$ requires C, 29·6; H, 2·5; N, 5·8%). It gave a yellow colour on diazotisation, followed by a red colour on coupling with dimethyl-α-naphthylamine, and a deep blue colour with dichloroquinonechloroimide and sodium hydrogen carbonate. It did not reduce cold silver nitrate.

Reduction of (III; R = NO_2) with ferrous hydroxide yielded a product which could not be purified since it rapidly darkened on exposure to air.

The author is grateful to Professor R. T. Williams for advice during the preparation of this paper.

Department of Biochemistry,
St. Mary's Hospital Medical School, London, W.2. [*Received, June 4th*, 1951.]

637. *The Isolation of 5-Methylcytosine Deoxyriboside from Wheat-germ Deoxyribonucleic Acid.*

By C. A. Dekker and D. T. Elmore.

5-Methylcytosine deoxyriboside has been isolated as its hydrochloride and picrate from enzymic hydrolysates of wheat-germ deoxyribonucleic acid by the combined techniques of ion exchange and partition chromatography. Physical data for this compound are recorded.

The general adherence of investigators in the nucleic acid field to the "tetranucleotide" theory, and lack, until recently, of suitable microanalytical methods, hindered the search for new components of the ribo- and deoxyribo-nucleic acids. Development of the chromatographic-separation and the spectral-analysis technique by Hotchkiss (*J. Biol. Chem.*, 1948, **175**, 315) and by Vischer and Chargaff (*ibid.*, 1948, **176**, 715) has now eliminated the latter obstacle and has provided elegant means for the quantitative determination of the purine and the pyrimidine degradation products of nucleic acids. Employing a relatively simple procedure, which combined a modification of the Vischer–Chargaff method for degradation and separation and the Markham–Smith (*Biochem. J.*, 1949, **45**, 294) photographic method for detection, Wyatt (*ibid.*, 1950, **47**, vii; *Nature*, 1950, **166**, 237) has demonstrated the presence of 5-methylcytosine in a variety of deoxypentose nucleic acids derived from both plant and animal sources. This pyrimidine base had very early been described by Johnson and Coghill (*J. Amer. Chem. Soc.*, 1925, **47**, 2838) as a constituent of tuberculinic acid, but the failure of Vischer, Zamenhof, and Chargaff (*J. Biol. Chem.*, 1949, **177**, 429), and of Wyatt (*locc. cit.*), to locate 5-methylcytosine in the hydrolysates of the deoxypentose nucleic acids of avian, human, and bovine tubercle bacilli, makes the validity of this early claim extremely doubtful. Furthermore, Wyatt was unable to confirm Rosedale's claim (*J. Ent. Soc. S. Africa*, 1948, **11**, 34) that in the nucleic acids of locusts and certain other insects thymine is quantitatively replaced by 5-methylcytosine. Pertinent to Wyatt's discovery, it should be mentioned that Hotchkiss (*loc. cit.*) and Daly, Allfrey, and Mirsky (*J. Gen. Physiol.*, 1950, **33**, 497), while examining the purine and pyrimidine base content of nucleic acids from various sources, obtained chromatographic evidence for the presence of a substance which had properties similar to those of cytosine. Although positive identification was not achieved, it now seems possible, in view of the chromatographic and spectral properties, that in each case the new base was 5-methylcytosine. Further evidence for the existence of this pyrimidine as an integral component of certain nucleic acids has come from ion-exchange studies by Cohn (*J. Amer. Chem. Soc.*, 1950, **72**, 2811). In an investigation of the nucleotides formed by enzymic degradation of a deoxypentose nucleic acid, a small quantity of a substance was isolated from which a base was derived, whose elution position and spectral properties suggested that it might be 5-methylcytosine. The existence of this new nucleotide has been more firmly established in a very recent paper (Cohn, *J. Amer. Chem. Soc.*, 1951, **73**, 1539).

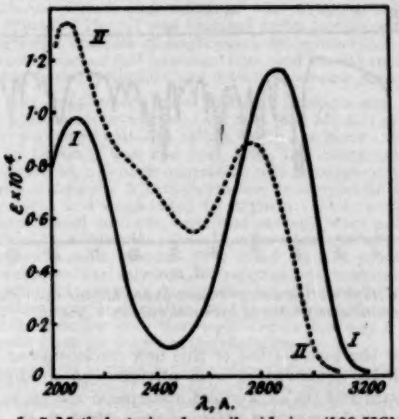
In view of the foregoing observations it was considered desirable to isolate and unequivocally identify 5-methylcytosine deoxyribonucleoside. Although this substance has not heretofore been isolated, evidence for its enzymic synthesis has been obtained by MacNutt (*Nature*, 1950, **166**, 444) in exchange reactions of 5-methylcytosine with purine deoxyribonucleosides. It was decided that the deoxyribonucleic acid isolated from wheat germ, which contains more 5-methylcytosine than any other nucleic acid so far investigated, would be the best source of the desired nucleoside. The deoxyribonucleic acid obtained was impure and contained up to 7% of ribonucleic acid, but removal of the latter was considered unnecessary for the present work. The presence of 5-methylcytosine was confirmed by paper-chromatographic examination of the formic acid hydrolysate (Vischer and Chargaff, *loc. cit.*; Wyatt, *locc. cit.*).

The nucleic acid was subjected to enzymic degradation, initially by deoxyribonuclease from beef pancreas (McCarty, *J. Gen. Physiol.*, 1946, **29**, 123), and then by the alkaline phosphatase of calf intestinal mucosa (Bielschowsky and Klein, *Z. physiol. Chem.*, 1932, **207**, 202; Klein, *ibid.*, 1938, **255**, 82). No attempt was made to inhibit the adenine deoxyriboside deaminase which is also present in calf intestinal mucosa. The amount of phosphorus split off as inorganic phosphate varied from 86 to 98%.

Nucleotides and most of the neutral nucleosides were removed by passing the hydrolysate down a column of "Zeo-Karb 215" in the H^+ cycle (Elmore, *Nature*, 1948, **161**, 931; *J.*, 1950,

2084; Harris and Thomas, *Nature*, 1948, **161**, 931; *J.*, 1948, 1936). The percolate appeared to contain deoxyribose as shown by paper chromatography, and it was concluded that purine deoxyribonucleosides were hydrolysed to the free bases during this process; this was considered desirable since it facilitated the isolation of the required nucleoside. Paper chromatography in *iso*propanol–2N-hydrochloric acid revealed that cytosine deoxyriboside, 5-methylcytosine deoxyriboside, guanine, hypoxanthine, and traces of thymidine and adenine were eluted from the column with aqueous ammonia. The purine bases were partly precipitated by alcohol; residual guanine and hypoxanthine and part of the adenine and thymidine were removed by chromatography on a cellulose column with *iso*propanol–2N-hydrochloric acid (65 : 35) as the solvent. Spectral analysis indicated that 5-methylcytosine deoxyriboside was present in the foremost fractions of those containing cytosine deoxyriboside. The absorption characteristics for 5-methylcytosine deoxyriboside were estimated from the data for the free pyrimidine (Hitchings, Elion, Falco, and Russell, *J. Biol. Chem.*, 1949, **177**, 357; Wyatt, *Nature*, 1950, **166**, 237), on the assumption that the carbohydrate on $N_{(3)}$ would produce a shift of $\lambda_{max.}$ towards the visible region of 20—50 Å in neutral or acid solution as has been observed for cytosine and cytidine (Ploeser and Loring, *J. Biol. Chem.*, 1949, **178**, 431). Adenine

FIG. 1.



I. 5-Methylcytosine deoxyriboside in N/100-HCl.
II. 5-Methylcytosine deoxyriboside in N/90-NaOH.

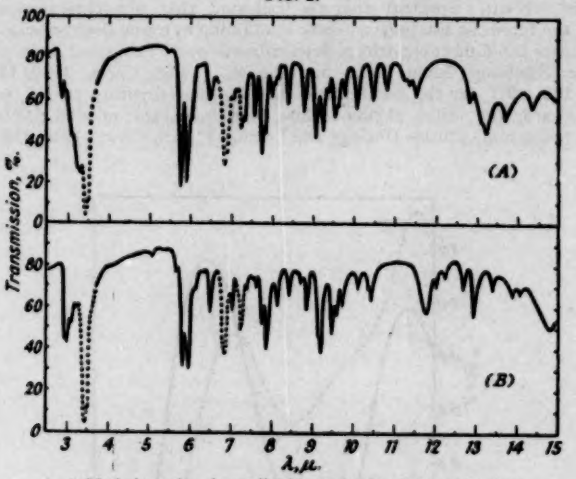
and thymidine were completely removed, and partial separation of cytosine deoxyriboside and 5-methylcytosine deoxyriboside was achieved by chromatography on a cellulose column with *n*-butanol saturated with water as the solvent. From those fractions, which were shown by paper chromatography to contain only 5-methylcytosine deoxyriboside, the nucleoside picrate, m. p. 175—178° (decomp.), was isolated. Most of the picrate was converted into the free nucleoside by percolation of an aqueous solution through a column of "Amberlite IRA-400." The product was somewhat hygroscopic and proved difficult to crystallise on account of its high solubility; the majority was therefore converted into the hydrochloride for ease of characterisation. An additional quantity of the hydrochloride was obtained from chromatographic fractions, which contained both cytosine deoxyriboside and 5-methylcytosine deoxyriboside, by further separation on a column of powdered cellulose, the upper layer of *n*-butanol–aqueous ammonia (*d* 0·88)–water (60 : 15 : 25) being used as the solvent system.

The ultra-violet and the infra-red absorption spectra are given in Figs. 1 and 2. The former confirms the prediction that the presence of a substituent on $N_{(3)}$ of 5-methylcytosine produces a shift of $\lambda_{max.}$ similar to that observed in the case of the cytosine nucleosides. Data are also given in Fig. 2 for cytosine deoxyriboside hydrochloride for comparison.

During an earlier attempt to isolate cytosine deoxyriboside and 5-methylcytosine deoxyriboside from an enzymic hydrolysate, neither could be detected by paper chromatography; instead, uracil deoxyriboside (Dekker and Todd, *Nature*, 1950, **166**, 557) and an increased amount of thymidine were present. These must have resulted from the adventitious action

of a deaminase. Since calf intestinal mucosa apparently does not contain a cytosine deoxyriboside deaminase (Klein, in Bamann and Myrbäck, " Die Methoden der Fermentforschung," New York, 1945), it must be concluded that bacterial contamination occurred at some stage. Certain strains of *Escherichia coli* are known to possess a powerful cytosine nucleoside deaminase (Wang, Sable, and Lampen, *J. Biol. Chem.*, 1950, **184**, 17). It is not known, however, if the same enzyme is responsible for the deamination of both cytosine and 5-methylcytosine deoxyribosides. In later experiments, protection of hydrolysates by toluene overcame this difficulty.

FIG. 2.



A. 5-Methylcytosine deoxyriboside hydrochloride in " Nujol."
B. Cytosine deoxyriboside hydrochloride in " Nujol."

Additional evidence for the formulation of this new nucleoside as 5-methylcytosine deoxyriboside was derived from its deamination with nitrous acid to thymidine, identified by its R_F on a paper chromatogram and its ultra-violet absorption spectrum. Furthermore, the new nucleoside gave a positive Dische reaction (*Mikrochemie*, 1930, **8**, 4).

EXPERIMENTAL.

All m.-p. determinations were made on the Kofler hot stage. Paper chromatograms were examined by means of a " Mineralite " lamp and subsequently photographed on Ilford Reflex Document Paper No. 50 in ultra-violet light (Markham and Smith, *loc. cit.*); fractions from cellulose columns were spotted on filter paper and examined under the " Mineralite " lamp. Ultra-violet absorption spectra were determined with a " Unicam " quartz spectrophotometer, Model S.P. 500. Infra-red absorption spectra were determined with a Perkin Elmer Instrument, Model 21, with rock salt optics.

Wheat-germ Deoxyribonucleic Acid.—Several batches of commercial wheat germ (" Froment ") were extracted by the method of Daly, Allfrey, and Mirsky (*loc. cit.*) and the nucleoprotein deproteinised by the method of Sevag, Lackmann, and Smolens (*J. Biol. Chem.*, 1938, **124**, 425). The product (2·0—5·2 g. per 36 oz. of " Froment ") was usually fibrous in nature (Found, in typical sample: C, 35·8; H, 5·3; N, 15·3%). The ribonucleic acid content was determined by Schneider's method (*ibid.*, 1945, **161**, 293) and shown to be not more than 7%.

Chromatographic Examination of Base Content.—Wheat-germ deoxyribonucleic acid (15 mg.) was heated with formic acid (1 c.c.) at 175° for 30—40 minutes. The hydrolysate was evaporated to dryness and dissolved in N-hydrochloric acid (0·2 c.c.). The filtered solution was qualitatively analysed by paper chromatography in *iso*propanol–5·7N-hydrochloric acid (65 : 35). The major constituents were guanine (R_F 0·31—0·34), adenine (R_F 0·45—0·48), cytosine (R_F 0·56—0·58), and thymine (R_F 0·81—0·83); 5-methylcytosine (R_F 0·64—0·66) and uracil (R_F = 0·72—0·74) were present in small quantity.

Enzymic Degradation.—Wheat-germ deoxyribonucleic acid (9·8 g.) was dissolved in distilled water (980 c.c.) and the pH adjusted to 7·0 with dilute aqueous ammonia. The solution was covered with toluene during all subsequent operations. Magnesium sulphate (2·27 g.) and crude deoxyribonuclease (50 mg.) were added and the solution incubated at 37—38° for 22 hours. The pH was then adjusted to 8·0 by the addition of N-aqueous ammonia (9 c.c.). N-Ammonia–N-ammonium sulphate buffer

(1 : 1; 100 c.c.) and calf intestinal mucosa extract (100 c.c.), prepared according to Klein's directions (*loc. cit.*), were introduced and the solution was incubated at 37—38° overnight. Magnesium sulphate (4 g.) and sufficient ammonia to bring the pH to 9·0 were added and the incubation was continued for a total of 47 hours. Magnesium ammonium phosphate was filtered off and sufficient barium hydroxide was added to precipitate sulphate ions quantitatively. Analysis of the filtrate for total phosphorus (Allen, *Biochem. J.*, 1940, **34**, 858) indicated that approx. 98% of the organic phosphate had been split off during the enzymic hydrolysis. The filtrate was evaporated under reduced pressure to 100 c.c. and then freeze-dried.

Isolation of Pyrimidine Deoxyribosides.—The dry residue was extracted with 8 portions (100 c.c.) of 95% ethanol. The filtered extracts were combined and analysed by paper chromatography in *iso*propanol–2N-hydrochloric acid (65 : 35). Purine deoxyribosides were hydrolysed to the free bases on the paper. The following substances were observed: guanine (R_F 0·26—0·31), hypoxanthine (R_F 0·36—0·42), adenine (R_F 0·40—0·47), cytosine deoxyriboside (R_F 0·58—0·63), 5-methylcytosine deoxyriboside (R_F 0·65—0·70), and thymidine (R_F 0·86—0·89). After evaporation of the ethanolic solution to dryness, the residue was dissolved in water (250 c.c.) and passed down a column (11·4 × 1·7 cm.) of "Zeo-Karb 215" (12 g.; 30—40 mesh). The column was washed with water (800 c.c.). From the combined percolate and washings, after evaporation under reduced pressure and addition of ethanol, crystalline thymidine (0·80 g.) was obtained, having m. p. 184—186° after one recrystallisation. The column was eluted with 0·5N-aqueous ammonia (3600 c.c.), and the eluate evaporated *in vacuo* to 75 c.c. Paper chromatography with *iso*propanol–2N-hydrochloric acid (65 : 35) revealed that most of the thymidine had been removed. Ethanol (150 c.c.) was added and the solution was placed in the refrigerator overnight. The precipitated purines were removed by filtration and washed with 66% aqueous ethanol. The combined filtrate and washings were evaporated under reduced pressure to 30 c.c. Precipitation with ethanol (170 c.c.) was repeated and a further small quantity of purines was removed. Paper chromatographic analysis in *iso*propanol–2N-hydrochloric acid (65 : 35) showed that the purine precipitate contained guanine and hypoxanthine, and the ethanolic filtrate was considerably enriched with respect to cytosine deoxyriboside and 5-methylcytosine deoxyriboside.

The ethanolic solution was evaporated under reduced pressure and freeze-dried. The residue (1·883 g.) was dissolved in *iso*propanol–2N-hydrochloric acid (65 : 35) and subjected to chromatography on a column (34 × 6 cm.) of powdered cellulose (350 g.) with the same solvent system, the automatic fraction collector described by Gilson (*Chem. and Ind.*, 1951, 185) being used. Paper chromatography of individual fractions revealed that, although separation was incomplete, the bulk of the purines had been removed. All fractions containing 5-methylcytosine deoxyriboside were combined, neutralised with aqueous sodium hydroxide, and evaporated to dryness. The residue was extracted with six portions (30 c.c. each) of *iso*propanol, and the combined extracts were evaporated to dryness. The residue (1·430 g.) was dissolved in *n*-butanol saturated with water (70 ml.). One fifth of the solution was subjected to chromatography on a column (29·4 × 3·3 cm.) of powdered cellulose (85 g.) with *n*-butanol saturated with water as the solvent. Thymidine and remaining traces of adenine were removed and partial separation of cytosine deoxyriboside and 5-methylcytosine deoxyriboside was effected, as revealed by spectroscopic examination and paper chromatography of relevant fractions. The remaining four-fifths of the mixture were then separated as above on a column (32·3 × 6·0 cm.) of powdered cellulose (350 g.) with a similar degree of fractionation.

Fractions from both separations containing only 5-methylcytosine deoxyriboside were combined and evaporated to small bulk. Ethanol (5 c.c.) and aqueous picric acid (7 c.c.) were added and the solution set aside in the refrigerator. *5-Methylcytosine deoxyriboside picrate* crystallised in fine needles and was recrystallised from ethanol. The yield was 3·0 mg. and the m. p. 175—177° (decomp.). A further quantity crystallised on storage in the refrigerator for several days. This was also recrystallised from ethanol [yield, 4·8 mg.; m. p. 175—178° (decomp.)] (Found: C, 41·0; H, 4·0. $C_{16}H_{15}O_{11}N_6$ requires C, 40·85; H, 3·9%).

The mother liquors from 5-methylcytosine deoxyriboside picrate were evaporated to dryness and the residue recrystallised from ethanol. The product (33·0 mg.) was passed in water (5 c.c.) down a column (2·0 × 0·6 cm.) of "Amberlite IRA-400." The column was washed thoroughly with water and the combined percolate and washings were evaporated under reduced pressure and freeze-dried. The residue was crystallised from ethanol–ether and afforded somewhat hygroscopic needles (8·2 mg.) of the free nucleoside. The mother-liquors were concentrated and saturated with dry hydrogen chloride. *5-Methylcytosine deoxyriboside hydrochloride* (8·0 mg.) crystallised in stout prisms, m. p. 156°.

All fractions from chromatographic separations containing both cytosine deoxyriboside and 5-methylcytosine deoxyriboside were combined, evaporated under reduced pressure, and freeze-dried. The residue (104·8 mg.) was dissolved in the upper layer of the solvent system *n*-butanol–aqueous ammonia (*d* 0·880)–water (60 : 15 : 25) and subjected to chromatography on a column (28·0 × 3·3 cm.) of powdered cellulose (80 g.), the same solvent being used. Paper chromatography of individual fractions revealed that a considerable degree of separation had been achieved. Fractions containing only 5-methylcytosine deoxyriboside were combined, concentrated, and freeze-dried. The residue (23·4 mg.) was converted into the picrate as above. The product (45 mg.) was converted into the free nucleoside on a column of "Amberlite IRA-400." A solution of the freeze-dried nucleoside (19·7 mg.) in ethanol–ether was saturated with dry hydrogen chloride, giving *5-methylcytosine deoxyriboside hydrochloride* (16·3 mg.), m. p. 156°, $[\alpha]_D^{18}$ +65° ±4° (*c*, 0·461 in N-sodium hydroxide) (Found: C, 42·1, 42·1; H, 5·7, 5·7; N, 13·6; Cl, 12·6. $C_{10}H_{14}O_4N_3Cl,\frac{1}{2}H_2O$ requires C, 41·9; H, 6·0; N, 14·6; Cl, 12·4%). Although the single nitrogen analysis is unsatisfactory, insufficiency of material precluded a duplicate determination. It is felt, however, in view of the other acceptable analyses and further evidence (crystallinity, sharp m. p., ultra-violet absorption spectra, and chromatographic homogeneity), that the substance is pure and has the structure designated. Ultra-violet light absorption: (i) in

N/100-hydrochloric acid: Maxima at 2860 and 2090 Å, $\epsilon_{max.}$ 11,610 and 9780; minimum at 2450 Å, $\epsilon_{min.}$ 1050; (ii) in N/90-sodium hydroxide: Maxima at 2770 and 2060 Å, $\epsilon_{max.}$ 8810 and 13,380; minimum at 2550 Å, $\epsilon_{min.}$ 5430.

All fractions from chromatographic separations containing only cytosine deoxyriboside were combined and evaporated under reduced pressure and the picrate isolated in the usual manner, the yield being 0·22 g. and the m. p. 208° (decomp.).

Deamination of 5-Methylcytosine Deoxyriboside.—The solution used for determination of optical rotation was acidified with acetic acid, and sodium nitrite was added. After several hours at room temperature, the solution was evaporated to dryness and the residue extracted with ethanol. Paper chromatography of the ethanol extract in *n*-butanol saturated with water revealed the presence of a considerable quantity of thymidine. The thymidine was extracted from the chromatogram with water, and the ultra-violet absorption spectrum determined: $\lambda_{max.}$ = 2680, $\lambda_{min.}$ = 2350 Å in neutral solution.

We are indebted to Prof. A. R. Todd, F.R.S., for his interest and advice. One of us (C. A. D.) was aided by a grant from the American Cancer Society, recommended by the Committee on Growth of the National Research Council. The other (D. T. E.) shared in this research during the tenure of a Beit Memorial Fellowship for Medical Research and was further assisted by a Scholarship from Roche Products, Ltd., to whom he expresses sincere thanks.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, May 30th,* 1951.]

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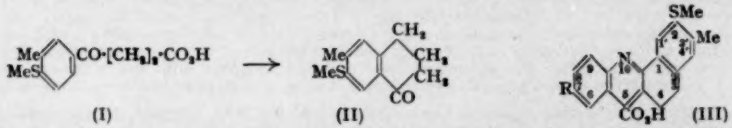
638. *Carcinogenic Nitrogen Compounds. Part VII.* 6-Methyl-7-methylthio-1-tetralone, and its Use in Syntheses of Nitrogenous Heterocyclic Compounds.*

By NG. PH. BUU-HOÏ and NG. HOÁN.

The preparation is described of 6-methyl-7-methylthio-1-tetralone from methyl *o*-tolyl sulphide by the succinic anhydride method. This ketone was used for the synthesis of acridine and carbazole compounds by known methods.

IN continuation of earlier investigations into the use of diversely substituted tetralones in the preparation of 1 : 2-benzacridines (Buu-Hoï, *J.*, 1946, 792) and benzocarbazoles (Buu-Hoï, Hoán, *et al.*, *J. Org. Chem.*, 1949, **14**, 492, 802; 1950, **15**, 511, 957, 962) for cancer research, we became interested in tetralones bearing sulphide groups (cf. Fieser and Wood, *J. Amer. Chem. Soc.*, 1940, **62**, 2674; 1941, **63**, 2323; Boyland, *Biochem. J.*, 1938, **32**, 1207; Berenblum, Kendall, and Orr, *ibid.*, 1936, **30**, 709). The present work deals with 6-methyl-7-methylthio-1-tetralone (III), a new ketone easily accessible from methyl *o*-tolyl sulphide by the standard succinic anhydride synthesis. β-(3-Methyl-4-methylthiobenzoyl)propionic acid (I) was converted by Kishner–Wolff–Huang-Minlon reduction (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) into γ-(3-methyl-4-methylthiophenyl)butyric acid, and by cyclisation with aluminium chloride into the tetralone (II). The yields were excellent, and the cyclisation was much smoother than that of γ-(*p*-



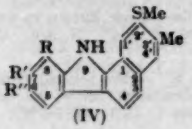
(I) (II) (III)

methylthiophenyl)butyryl chloride owing to the *para*-directing influence of the additional methyl group. The cyclic ketones thus obtained condensed readily with aromatic aldehydes (and with furfuraldehyde), to give a series of crystalline 2-arylidene-6-methyl-7-methylthio-1-tetralones, giving deep halochromic colours with sulphuric acid (see Table, p. 2870).

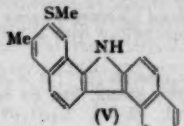
In view of the strychnine-like activity (von Braun, *Annalen*, 1926, **451**, 1) and analeptic properties of 1 : 2-dihydro-3 : 4-benzacridine-9-carboxylic acid ("Tetrophan") and of similar sulphur-containing compounds (Buu-Hoï and Royer, *Compt. rend.*, 1946, **223**, 806), 6-methyl-7-methylthio-1-tetralone was combined with isatin and 5-bromoisatin to give 3 : 4-dihydro-3′-methyl- (V; R = H) and 7-bromo-3 : 4-dihydro-3′-methyl-2′-methylthio-1 : 2-benzacridine-5-carboxylic acid (V; R = Br).

* Part VI, *J.*, 1951, 795.

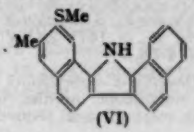
The activity of angular benzocarbazoles and dibenzocarbazoles as tumour-producing agents (cf. Boyland and Brues, *Proc. Roy. Soc.*, 1937, *B*, **122**, 429; Schürch and Winterstein, *Z. physiol. Chem.*, 1935, **236**, 79; Lacassagne, Buu-Hoï, Royer, and Zajdela, *Compt. rend. Soc. biol.*, 1947, **141**, 635) led us to prepare similar compounds from (II). Its arylhydrazones were converted by hydrogen chloride in acetic acid into 3 : 4-dihydrocarbazoles, which were subsequently dehydrogenated by means of chloranil. Thus was obtained a series of 1 : 2-benzocarbazoles (IV). A similar synthesis performed with the 2-diphenylylhydrazone



(IV)



(V)



(VI)

probably gave 3′-methyl-2′-methylthio-8-phenyl-1 : 2-benzocarbazole (VI; R = Ph, R′ = R″ = H), although the alternative cyclisation into the 2′-position of the diphenyl residue is not excluded. The pentacyclic compounds (V) and (VI) were easily prepared by dehydrogenation of their corresponding 3 : 4-dihydro-derivatives.

Experimental.

β-(3-Methyl-4-methylthiobenzoyl)propionic Acid.—Methyl *o*-tolyl sulphide (b. p. 207°) was prepared in >96% yield from *o*-thiocresol with methyl sulphate and potassium hydroxide. To an ice-cooled, well-stirred mixture of this sulphide (69 g.) and succinic anhydride (60 g.) with dry nitrobenzene (300 c.c.), powdered aluminium chloride (150 g.) was added in small portions; the mixture was kept over-night at room temperature and then poured on ice, and the nitrobenzene removed with steam. The solid, obtained after cooling, was treated with boiling aqueous sodium carbonate; after filtration and acidification with dilute hydrochloric acid, a 98% yield of the crude *acid* (I) was obtained; recrystallisation from benzene gave fine shiny colourless needles, m. p. 136° (Found : C, 60·3; H, 5·9; S, 13·1. $C_{12}H_{14}O_3S$ requires C, 60·5; H, 5·9; S, 13·4%).

γ-(3-Methyl-4-methylthiophenyl)butyric Acid.—A solution of the foregoing keto-acid (110 g.) in a mixture of 85% hydrazine hydrate (90 g.), potassium hydroxide (90 g.), and diethylene glycol (350 c.c.) was heated with removal of water until the temperature reached 190—195°, and refluxed for a further 2 hours. After cooling, the reaction mixture was diluted with water, and yielded on acidification with dilute hydrochloric acid an oil which was taken up in chloroform. The chloroform solution was dried (Na_2SO_4) and the solvent removed; the solid residue (103 g.) crystallised from ligroin (b. p. 80—120°) in shiny colourless leaflets, m. p. 52° (Found : C, 64·2; H, 7·2. $C_{11}H_{14}O_2S$ requires C, 64·3; H, 7·1%).

6-Methyl-7-methylthio-1-tetralone.—Redistilled thionyl chloride (60 g.) was cautiously added in small portions to the foregoing *acid* (100 g.), and the mixture kept overnight at room temperature. The oil obtained after removal of thionyl chloride on a water-bath was dissolved in dry carbon disulphide (350 c.c.), and powdered aluminium chloride (68 g.) was added in small portions with ice-cooling. After 5 hours at room temperature, the mixture was poured on ice, the organic layer washed thoroughly with 5% aqueous sodium hydroxide, then with water, and dried (Na_2SO_4), the solvent removed, and the residue vacuum-fractionated. This yielded the *tetralone* (76 g.), b. p. 210—218°/15 mm., crystallising from methanol in fine colourless prisms, m. p. 65°, and giving an orange colour with sulphuric acid (Found : C, 69·8; H, 6·9; S, 15·1. $C_{13}H_{16}OS$ requires C, 69·9; H, 6·8; S, 15·5%). The semicarbazone crystallised from ethanol in shiny needles, m. p. 251°; the thiosemicarbazone (prepared in acetic acid) formed from acetic acid a microcrystalline powder, m. p. 201°.

3 : 4-Dihydro-3′-methyl-2′-methylthio-1 : 2-benzacridine-5-carboxylic Acid (III; R = H).—A mixture of the ketone (II) (2 g.), isatin (1·7 g.), and a solution of potassium hydroxide (1·7 g.) in water (2 c.c.)–ethanol (20 c.c.) was refluxed for 12 hours; after dilution with water and removal of impurities by ether-extraction, the aqueous layer was slightly acidified with acetic acid. The yellow precipitate (2 g.) was recrystallised from methanol, yielding long yellow needles which softened at about 235°, but did not liquefy completely until 288° (Found : N, 4·2. $C_{20}H_{17}O_2NS$ requires N, 4·1%).

7-Bromo-3 : 4-dihydro-3′-methyl-2′-methylthio-1 : 2-benzacridine-5-carboxylic Acid (III; R = Br).—Similarly prepared from the ketone (II) (2 g.), 5-bromoisatin (2·5 g.), and potassium hydroxide (1·7 g.), this *acid* formed from ethanol fine yellow needles, m. p. >320° (Found : N, 3·0; Br, 19·0. $C_{20}H_{16}O_2NSBr$ requires N, 3·4; Br, 19·3%). Decarboxylation by heat gave 7-bromo-3 : 4-dihydro-3′-methyl-2′-methylthio-1 : 2-benzacridine, characterised as its *picrate*, which formed from xylene fine orange prisms, m. p. 248° (decomp.), sublimable at >210° (Found : N, 9·0. $C_{25}H_{19}O_7N_4SBr$ requires N, 9·3%).

3 : 4-Dihydro-3′-methyl-2′-methylthio-1 : 2-benzocarbazole.—A solution of the ketone (II) (2·2 g.) and phenylhydrazine (2 g.) in ethanol (40 c.c.) was refluxed for 1 hour. After cooling and addition of water, the crude phenylhydrazone was collected and cyclised by a few minutes' heating with a solution of hydrogen chloride in acetic acid (20 c.c.). The reaction product was poured into water and the *benzocarbazole* was collected, dried, and recrystallised from ligroin (b. p. 80—120°), giving a 92% yield

of fine colourless needles, m. p. 157° (Found: C, 77·3; H, 6·0. $C_{18}H_{17}NS$ requires C, 77·4; H, 6·1%), and giving an orange-yellow colour with sulphuric acid, and a violet picrate.

3'-Methyl-2'-methylthio-1 : 2-benzocarbazole (IV; R = R' = R'' = H).—A solution of the foregoing compound (1 g.) and chloranil (1·1 g.) in dry xylene (25 c.c.) was gently refluxed for 6 hours. After cooling and filtration from tetrachloroquinol, the solution was washed with 10% aqueous sodium hydroxide, then with water, and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the solid residual *carbazole* recrystallised twice from benzene, giving shiny colourless leaflets (90%), m. p. 218° (orange-red colour with sulphuric acid) (Found: C, 78·0; H, 5·6. $C_{18}H_{15}NS$ requires C, 77·9; H, 5·4%). The corresponding picrate formed from ethanol fine shiny violet needles, m. p. 220°.

3 : 4-Dihydro-3' : 6-dimethyl-2'-methylthio-1 : 2-benzocarbazole crystallised from ligroin in fine colourless leaflets, m. p. 167°, giving an orange colour with sulphuric acid (Found: N, 4·6. $C_{19}H_{19}NS$ requires N, 4·7%).

3' : 6-Dimethyl-2'-methylthio-1 : 2-benzocarbazole (IV; R = R' = H, R'' = Me) formed, from ligroin, colourless microscopic needles, m. p. 223°, giving, like its isomers described below, an orange-red colour with sulphuric acid (Found: C, 78·1; H, 5·6. $C_{19}H_{17}NS$ requires C, 78·3; H, 5·8%).

3 : 4-Dihydro-3' : 7-dimethyl-2'-methylthio-1 : 2-benzocarbazole.—Obtained in 85% yield as apparently the sole product from the *m*-tolylhydrazone of the ketone (II), a reaction which could theoretically be expected to give two isomeric products, this *compound* formed, from ligroin, fine colourless needles, m. p. 155° (Found: N, 4·5%).

3' : 7-Dimethyl-2'-methylthio-1 : 2-benzocarbazole (IV; R = R'' = H, R' = Me) crystallised from benzene–ligroin in grey-tinged prisms, m. p. 199° (Found: C, 78·0; H, 6·0%).

3' : 8-Dimethyl-2'-methylthio-1 : 2-benzocarbazole (IV; R = Me, R' = R'' = H).—The corresponding 3 : 4-dihydro-compound was not isolated in a pure form. The dehydrogenation *product* crystallised from ligroin in microscopic grey-tinged needles, m. p. 189° (Found: C, 78·1; H, 6·0%).

3'-Methyl-2'-methylthio-8-phenyl-1 : 2-benzocarbazole (?) (IV; R = Ph, R' = R'' = H) formed, from ligroin, fine colourless needles, m. p. 177° (Found: C, 81·4; H, 5·1. $C_{24}H_{19}NS$ requires C, 81·5; H, 5·3%).

3 : 4-Dihydro-3'-methyl-2'-methylthio-1 : 2-5 : 6-dibenzocarbazole.—Obtained in 87% yield, this *derivative* formed, from ligroin, fine yellowish needles, m. p. 183°, giving an orange-red colour with sulphuric acid (Found: N, 4·2. $C_{23}H_{19}NS$ requires N, 4·2%).

3'-Methyl-2'-methylthio-1 : 2-5 : 6-dibenzocarbazole (V) formed from benzene almost colourless microscopic needles, m. p. 232° (Found: C, 80·7; H, 5·3. $C_{23}H_{17}NS$ requires C, 81·0; H, 5·2%), giving a brown-red colour with sulphuric acid, and a brownish-violet picrate.

3 : 4-Dihydro-3'-methyl-2'-methylthio-1 : 2-7 : 8-dibenzocarbazole, obtained in 90% yield, formed, from benzene–ligroin, fine colourless leaflets, m. p. 148°, giving an orange-red colour with sulphuric acid (Found: N, 4·0%).

3'-Methyl-2'-methylthio-1 : 2-7 : 8-dibenzocarbazole (VI) formed from benzene fine grey-tinged needles, m. p. 204°, giving a brown-red colour with sulphuric acid (Found: C, 80·8; H, 5·2. $C_{23}H_{17}NS$ requires C, 81·0; H, 5·2%), and a brown-violet picrate.

Condensation of Aldehydes with the Ketone (II).—The procedure was that generally used for the preparation of chalcones: equimolecular amounts of the ketone and the appropriate aldehyde were dissolved in the minimum volume of ethanol, and the solution shaken with some drops of a 40% aqueous solution of sodium or potassium hydroxide. The precipitate formed after cooling was collected, and recrystallised twice from ethanol, except for the derivative from furfuraldehyde which was recrystallised from methanol. The *compounds* prepared are listed in the Table.

2-Arylidene-6-methyl-7-methylthio-1-tetralones.

Arylidene radical	M. p.	Colour with H_2SO_4	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
2-Furfurylidene *	95°	scarlet	$C_{17}H_{16}O_2S$	71·6	5·5	71·8	5·6
p-C_6H_4Cl·CH:	156	orange-red	$C_{19}H_{17}OSCl$	69·1	5·2	69·4	5·1
o-C_6H_4Cl·CH:	149	brown-red	"	69·5	5·3	69·4	5·1
2 : 4 : 1-$C_6H_3Cl_2$·CH:	135	orange-brown	$C_{19}H_{16}OSCl_2$	62·5	4·5	62·8	4·4
3 : 4 : 1-$C_6H_3Cl_2$·CH:	145	dark red	"	62·8	4·6	62·8	4·4
m-NO_2·C_6H_4·CH:	178	brown	$C_{19}H_{17}O_3NS$	67·0	5·2	67·2	5·0
p-OMe·C_6H_4·CH:	146	blood red	$C_{20}H_{20}O_2S$	74·1	6·4	74·0	6·1
3 : 4 : 1-$(OMe)_2C_6H_3$·CH:	148	crimson	$C_{21}H_{22}O_2S$	71·1	6·4	71·2	6·2
3 : 4 : 1-$(CH_2O_2)C_6H_3$·CH:	137	violet-red	$C_{20}H_{18}O_2S$	70·8	5·4	71·0	5·3
3-Pyrenylmethylene	214	blue	$C_{28}H_{22}OS$	83·3	5·0	83·2	5·2

* The first five compounds formed long, almost colourless needles, the four following ones formed long yellow needles, and the last one formed fine, bright yellow prisms.

DEPARTMENT OF ORGANIC CHEMISTRY,
THE RADIUM INSTITUTE, UNIVERSITY OF PARIS.

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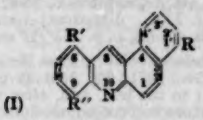
639. *Carcinogenic Nitrogen Compounds. Part VIII.* Further Syntheses of Hydroxybenzacridines and Hydroxydibenzacridines.*

By Ng. Ph. Buu-Hoï.

In continuation of earlier work, several new 3 : 4-benzacridines, and 1 : 2-6 : 7- and 3 : 4-6 : 7-dibenzacridines bearing one or two hydroxy- or alkoxy-groups, have been synthesised by known methods for biological examination. Incidentally, the chemistry of some dihydroxynaphthalenes was more closely investigated, and several new derivatives were prepared. Monomethylation of 1 : 6-dihydroxynaphthalene was shown to yield 5-methoxy-2-naphthol, in accordance with the theory relating reactivity to π-electron densities.

Recently, the synthesis was described of several angular hydroxybenzacridines required for preliminary experiments with compounds similar to expected metabolites of the carcinogenic 1 : 2- and 3 : 4-benzacridines (Buu-Hoï, *J.*, 1950, 2096). The present work extends this research to two further new substitution products of 3 : 4-benzacridine, *viz.*, the 1′- (I; R = OH, R′ = R″ = H) and the 9-hydroxy-derivative (I; R = R′ = H, R″ = OH). The first isomer was obtained by demethylation of the corresponding methyl ether, the product from an Ullmann–Fetvadjian reaction (*Ber.*, 1903, **36**, 1029) between β-naphthol, *o*-anisidine, and paraformaldehyde. 9-Hydroxy-3 : 4-benzacridine is far lower-melting and more soluble than the isomerides hitherto known, properties apparently caused by intramolecular hydrogen bonding as shown in (II). Like 8-hydroxyquinoline and 1-hydroxyacridine, it readily gave chelation products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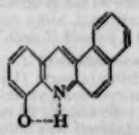
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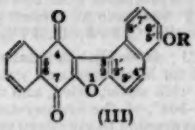
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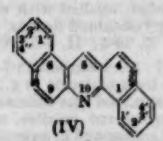
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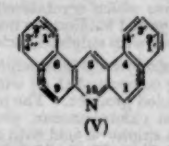
(V)

with the cations of a wide series of metals, and is also more strongly antibacterial against *Staphylococcus aureus* than its non-chelating isomerides, two properties which might well be linked (cf. Albert, "The Acridines," London, 1951, p. 259). The similar synthesis of 1′-hydroxy-3 : 4-benzacridine, starting from aniline, paraformaldehyde, and 5-methoxy-2-naphthol, was of interest because it involved an investigation of the constitution of monoalkylation products of 1 : 6-dihydroxynaphthalene. For instance, monomethylation with one molecule of methyl sulphate in the presence of one molecule of potassium hydroxide would yield 5-methoxy-2-naphthol, 6-methoxy-1-naphthol, or a mixture of the two. In fact, the first substance was formed, as the reaction product gave a sharp-melting picrate and reacted readily with one molecule of 2 : 3-dichloro-1 : 4-naphthaquinone to give the compound (III; R = Me). Such a reaction, observed by Eistert for β-naphthol itself (*Ber.*, 1947, **80**, 52), and more recently extended to its 6-substituted derivatives (Buu-Hoï, Le Bihan, and Binon, *J. Org. Chem.*, 1951, **16**, 185), is now found to be highly characteristic of 2-naphthols having their 1-position free, and not to occur with 1-naphthols. The constitution of our brasan derivative was proved by the identity of its demethylation product with the 1′-hydroxy-compound (III; R = H) prepared directly from 1 : 6-dihydroxynaphthalene.

2 : 6-Dimethoxyaniline underwent readily an Ullmann–Fetvadjian reaction with β-naphthol and paraformaldehyde, to give 6 : 9-dimethoxy-3 : 4-benzacridine (I; R = H, R′ = R″ = OMe); demethylation afforded, apparently, 6 : 9-dihydroxy-3 : 4-benzacridine (I; R = H, R′ = R″ = OH), but its instability prevented complete purification.

Whereas some 5-hydroxyaryldibenzacridines are already known (Buu-Hoï, *J.*, 1950, 2096), no dibenzacridines bearing *Bz*-hydroxy- or -ether groups have yet been described. Of the thir-

* Part VII, preceding paper.

teen possible monohydroxy-derivatives of 1 : 2-6 : 7-dibenzacridine (IV), five have now been prepared by a method analogous to that employed earlier, *viz.*, 2′-, 4′-, 2″-, 3″-, and 4″-hydroxy-1 : 2-6 : 7-dibenzacridine. In the 3 : 4-6 : 7-dibenzacridine series (V), the 1′-, 2′-, and 3′-hydroxy-derivatives were prepared.

All these hydroxydibenzacridines were very similar to each other and to the hydroxy-3 : 4-benzacridines already described. No such compounds have yet been detected in the urine and fæces of animals fed with the carcinogenic 1 : 2-6 : 7- and 3 : 4-6 : 7-dibenzacridines.

Experimental.

9-Hydroxy-3 : 4-benzacridine.—To a boiling mixture of β-naphthol (20 g.) and *o*-anisidine (15 g.), paraformaldehyde (3 g.) was cautiously added in small portions. The reaction product was boiled for 5 minutes in the air to complete the dehydrogenation of the intermediary acridan formed. A mixture of the crude 9-methoxy-3 : 4-benzacridine (15 g.), obtained on vacuum-distillation (b. p. 280—285°/15 mm.), and pyridine hydrochloride (50 g.) was boiled for 10 minutes. After the product had cooled, water (250 c.c.) was added, and the orange-yellow precipitate of 9-hydroxy-3 : 4-benzacridine hydrochloride obtained on scratching with a glass rod was collected and decomposed with dilute aqueous ammonia. *9-Hydroxy-3 : 4-benzacridine* (8 g.) formed, from benzene, greenish-yellow silky needles, m. p. 159—160°, which dissolved readily in aqueous sodium hydroxide with a yellow colour (Found: C, 83·1; H, 4·1. $C_{17}H_{11}ON$ requires C, 83·2; H, 4·4%). An attempt to prepare the isomeric 9-hydroxy-1 : 2-benzacridine in the same way from α-naphthol, *o*-anisidine, and paraformaldehyde failed.

Methylation of 1 : 6-Dihydroxynaphthalene.—A suspension of 1 : 6-dihydroxynaphthalene (32 g.) and methyl sulphate (30 g.) in water was treated with concentrated aqueous potassium hydroxide (12 g.), in small portions, with vigorous shaking. The shaking was continued for a few minutes, some more alkali was added, and the reaction product was extracted with ether. The dark oil obtained on acidification with hydrochloric acid of the aqueous layer was taken up in ether and dried (Na_2SO_4), the solvent removed, and the residue distilled in a vacuum. *5-Methoxy-2-naphthol* (23 g.) formed a pale yellow viscous oil, b. p. 208—210°/20 mm., which did not solidify on prolonged storage in the refrigerator and darkened rapidly on exposure to air (Found: C, 75·7; H, 5·8. $C_{11}H_{10}O_2$ requires C, 75·9; H, 5·7%). The picrate formed, from ethanol, silky orange-red needles, m. p. 172°. 6-Methoxy-1-naphthol had been summarily recorded in a patent (*Chem. Centr.*, 1921, II, 504) as a solid, b. p. 185°/12 mm.

5′-Methoxy-5 : 6-benzonaphtho(2′ : 1′-2 : 3)coumarone-4 : 7-quinone (III; R = Me).—A mixture of 2 : 3-dichloro-1 : 4-naphthaquinone (Ullmann and Ettisch, *Ber.*, 1921, **54**, 259) (2 g.), 5-methoxy-2-naphthol (2 g.), and anhydrous pyridine (12 c.c.) was brought to the boil, and, after the violent initial reaction had subsided, refluxed for 30 minutes. After the mixture had cooled, methanol was added, and the *quinone* which crystallised was collected, washed with water, and recrystallised from toluene. The fine orange-red sublimable needles (2·5 g.) obtained had m. p. 261—262° and gave an intense greenish-blue colour with sulphuric acid (Found: C, 76·5; H, 3·6. $C_{21}H_{12}O_4$ requires C, 76·8; H, 3·7%).

5′-Hydroxy-5 : 6-benzonaphtho(2′ : 1′-2 : 3)coumarone-4 : 7-quinone (III; R = H).—A mixture of the foregoing compound (1 g.) with pyridine hydrochloride (8 g.) was boiled for 5 minutes, and water added to the cooled product. The precipitate obtained was collected, washed with water, dried, and recrystallised from chlorobenzene, giving fine brown-red needles, m. p. 303—304°, of the *hydroxy*-compound, soluble in sulphuric acid with a deep blue colour and in aqueous sodium hydroxide to give deep violet-blue solutions (Found: C, 76·0; H, 3·1. $C_{20}H_{10}O_4$ requires C, 76·4; H, 3·1%). The same product was obtained directly by refluxing for 2 hours a mixture of 1 : 6-dihydroxynaphthalene (2 g.), 2 : 3-dichloro-1 : 4-naphthaquinone (1·9 g.), and pyridine (12 c.c.).

6 : 9-Dimethoxy-3 : 4-benzacridine.—A mixture of β-naphthol (20 c.), and 2 : 6-dimethoxyaniline (15 g.) was treated with paraformaldehyde (2·5 g.) in the usual way. *6 : 9-Dimethoxy-3 : 4-benzacridine*, the fraction boiling at 302—306°/15 mm. (12 g.), crystallised from methanol in long yellow silky needles, m. p. 168°, giving with sulphuric acid a brown-red colour (Found: C, 78·8; H, 5·1. $C_{19}H_{15}O_2N$ requires C, 78·9; H, 5·2%). The picrate formed from nitrobenzene shiny orange-red needles, m. p. *ca.* 267—269° (decomp.). Five minutes' refluxing of a mixture of 6 : 9-dimethoxy-3 : 4-benzacridine (2 g.) and pyridine hydrochloride (15 g.) yielded after cooling a brown water-insoluble hydrochloride; on treatment with dilute aqueous ammonia, this gave a greenish product, which dissolved readily in aqueous caustic alkalis with a deep yellow colour, and was probably 6 : 9-dihydroxy-3 : 4-benzacridine but could not be purified sufficiently for analysis.

1′-Hydroxy-3 : 4-benzacridine (I; R = OH, R′ = R″ = H).—This *compound* formed from nitrobenzene fine pale yellow, sublimable needles, m. p. 275° (Found: C, 83·0; H, 4·6. $C_{17}H_{11}ON$ requires C, 83·2; H, 4·4%). The corresponding *methyl ether* formed, from ethanol, long silky pale yellow needles, m. p. 172° (Found: N, 5·4. $C_{18}H_{13}ON$ requires N, 5·4%), giving an orange picrate (silky needles from nitrobenzene), m. p. 289—290°.

4″-Methoxy-1 : 2-6 : 7-dibenzacridine.—To a boiling mixture of 5-methoxy-2-naphthol (5 g.) and α-naphthylamine (4·5 g.), paraformaldehyde (1 g.) was added in small portions. The thick orange *ether* boiling above 300°/12 mm. (4 g.) crystallised readily from benzene in pale yellow silky needles, m. p. 214°, giving with sulphuric acid a deep yellow colour (Found: C, 85·1; H, 4·8. $C_{22}H_{13}ON$ requires C, 85·4; H, 4·8%).

4″-Hydroxy-1 : 2-6 : 7-dibenzacridine.—The usual demethylation of the foregoing compound yielded a water-insoluble red hydrochloride; the free *4″-hydroxy-1 : 2-6 : 7-dibenzacridine* obtained on basification with dilute aqueous ammonia formed, from nitrobenzene, yellowish silky, sublimable needles, m. p. 304—305°, whose alkaline solutions were deep yellow (Found: C, 85·2; H, 4·5. $C_{21}H_{13}ON$ requires C, 85·4; H, 4·4%).

3''-*Hydroxy*-1 : 2-6 : 7-*dibenzacridine*.—The 6-methoxy-2-naphthol used for this synthesis was prepared by monomethylation of 2 : 6-dihydroxynaphthalene according to Fischer and Hammerschmidt (*J. pr. Chem.*, 1916, **94**, 24). **3''-*Hydroxy*-1 : 2-6 : 7-*dibenzacridine*** formed from nitrobenzene fine greenish-yellow needles, melting above 330° (Found : C, 85·1; H, 4·2%), giving an orange-red water-insoluble hydrochloride. The corresponding ***methyl ether*** crystallised from benzene in shiny pale yellow needles, m. p. 181—182° (Found : N, 4·5. $C_{23}H_{15}ON$ requires N, 4·5%).

2''-*Hydroxy*-1 : 2-6 : 7-*dibenzacridine*.—The 7-methoxy-2-naphthol used was prepared by monomethylation of 2 : 7-dihydroxynaphthalene; **2''-*hydroxy*-1 : 2-6 : 7-*dibenzacridine*** formed, from nitrobenzene, yellow needles, m. p. 271—272° (Found : C, 85·2; H, 4·6%), giving with aqueous sodium hydroxide yellow solutions, and brown-red ones with alcoholic sodium hydroxide; the hydrochloride formed orange-yellow needles, insoluble in water. The ***methyl ether*** crystallised from benzene in pale yellow fluffy needles, m. p. 209—210° (Found : C, 85·4; H, 5·0%).

4'-*Hydroxy*-1 : 2-6 : 7-*dibenzacridine*.—5-Methoxy-1-naphthylamine (12 g.) was prepared from 5-amino-1-naphthol (16 g.), methyl sulphate (15 g.), and sodium hydroxide (5 g.); **4'-*hydroxy*-1 : 2-6 : 7-*dibenzacridine*** formed from nitrobenzene fine greenish-yellow needles, m. p. 295—296° (Found : C, 85·1; H, 4·8%), giving a red hydrochloride and dissolving in aqueous sodium hydroxide with an intense yellow colour. **4'-*Methoxy*-1 : 2-6 : 7-*dibenzacridine*** formed from benzene silky pale yellow needles, m. p. 210° (Found : C, 85·2; H, 4·9%), and gave a picrate crystallising from nitrobenzene in shiny orange prisms, m. p. 268—269°.

4'-*Allyloxy*-1 : 2-6 : 7-*dibenzacridine* (cf. Buu-Hoï, *J.*, 1950, 2006) formed, from benzene, pale yellow silky needles, m. p. 195—196° (Found : N, 4·1. $C_{26}H_{17}ON$ requires N, 4·2%).

2'-*Hydroxy*-1 : 2-6 : 7-*dibenzacridine*.—The 7-methoxy-1-naphthylamine (b. p. 192—193°/14 mm.) was prepared from methyl sulphate, sodium hydroxide, and 1-amino-2-naphthol; **2'-*hydroxy*-1 : 2-6 : 7-*dibenzacridine*** formed, from nitrobenzene, fine pale yellow needles, m. p. 258° (Found : C, 85·2; H, 4·6%). The corresponding methyl ether crystallised from ethanol in pale yellow fluffy needles, m. p. 181—182°.

1'-*Methoxy*-3 : 4-6 : 7-*dibenzacridine*.—Obtained in 40% yield from 5-methoxy-2-naphthol (5 g.), β-naphthylamine (5 g.), and paraformaldehyde (1 g.), this ***ether*** crystallised from ethanol–benzene as shiny silky yellowish needles, m. p. 239—240° (Found : N, 4·2%). **1'-*Hydroxy*-3 : 4-6 : 7-*dibenzacridine*** formed from nitrobenzene fine yellow needles, m. p. 285° (Found : C, 85·2; H, 4·5%).

2'-*Hydroxy*-3 : 4-6 : 7-*dibenzacridine* formed, from nitrobenzene, greenish-yellow prisms, m. p. >340° (Found : C, 85·1; H, 4·6%), giving a hydrochloride which was readily hydrolysed. The isomeric **3'-*hydroxy*-3 : 4-6 : 7-*dibenzacridine*** crystallised from nitrobenzene in velvety yellow needles, m. p. 332—333° (decomp.) (Found : C, 85·2; H, 4·4%).

This work is part of a cancer research scheme, carried out under Professor A. Lacassagne, with the financial support of the United States Public Health Service (Federal Security Agency). The author thanks the authorities concerned, Light Chemicals Ltd. (Colnbrook) for supplies of dihydroxynaphthalenes and aminonaphthols, and Miss P. F. Boshell, M.A. (Oxon.), for help with the work.

THE RADIUM INSTITUTE, UNIVERSITY OF PARIS. [*Received, June 27th*, 1951.]

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640. *Some Glycosylbenziminazoles.*

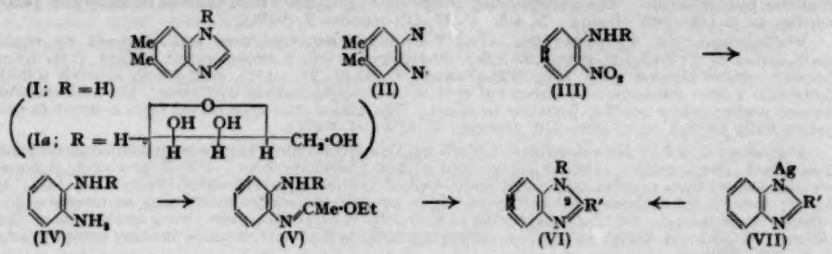
By H. ANTAKI and V. PETROW.

With the object of preparing metabolite inhibitors of vitamin B_{12} for study as potential chemotherapeutic agents, the synthesis of (i) 5-chloro- and 5 : 6-dichloro-1-glycosylbenziminazole and (ii) 2-methyl- and 2 : 5-dimethyl-1-glycosylbenziminazole (the " *N*-glycosides ") has been undertaken.

Compounds of type (ii) were prepared by a novel route in which a *N*-glycosyl-*o*-phenylenediamine is treated with ethyl orthoacetate, and the resulting *iso*acetanilide is converted into the glycosylbenziminazole by treatment with dilute hydrochloric acid.

THE isolation of 5 : 6-dimethylbenziminazole (I) (Brink and Folkers, *J. Amer. Chem. Soc.*, 1949, **71**, 2951; Holiday and Petrow, *J. Pharm. Pharmacol.*, 1949, **1**, 734; Beaven, Holiday, Johnson, Ellis, Mamalis, Petrow, and Sturgeon, *ibid.*, p. 957; Brink and Folkers, *J. Amer. Chem. Soc.*, 1950, **72**, 4442) and 5 : 6-dimethyl-1-α-D-ribofuranosylbenziminazole (5 : 6-dimethylbenziminazole-1-α-D-ribofuranoside) (I*a*) (Brink, Holly, Shunk, Peel, Cahill, and Folkers, *ibid.*, p. 1866; see also Cooley, Ellis, Mamalis, Petrow, and Sturgeon, *J. Pharm. Pharmacol.*, 1950, **2**, 579) from vitamin B_{12} makes it possible to draw a structural analogy between riboflavin and the " benziminazole glycoside " portion of the B_{12} molecule, and to postulate the existence of a common biogenetic precursor of the two vitamins containing the grouping (II). By a further extension of the concept it is reasonable to conclude that those structural alterations which effect conversion of riboflavin into a metabolite inhibitor of riboflavin would likewise be effective in the benziminazole glycoside series.

The preparation of a riboflavin antagonist had been effected fortuitously by Kuhn, Weygand, and Möller (*Ber.*, 1943, **76**, 1044), who, having noted the crystallographic similarity between methyl- and chloro-substituted benzene derivatives, prepared 6 : 7-dichloro-9-1′-D-ribityl*iso*-



alloxazine for biological study. This compound, in striking contrast with the parent vitamin, proved to be a potent metabolite inhibitor. Its 6 : 7-dibromo-analogue, however, exhibited only one-quarter to one-eighth of the activity of the corresponding dichloro-compound (Weygand, Löwenfeld, and Möller, *ibid.*, 1951, **84**, 101), an observation which emphasises the importance of atomic volume in relation to biological effect. Replacement of methyl by chlorine in riboflavin thus leads to complete reversal in the biological functions. Properly constituted analogues of (Ia), such as 5-chloro- and 5 : 6-dichloro-1-glycosylbenziminazole may, on this basis, be expected to function as B_{12}-antagonists, the preparation of which formed the object of the present study.

Our second approach to the problem of B_{12}-inhibitors derived from the observation of Emerson, Brink, Holly, Koniuszy, Heyl, and Folkers (*J. Amer. Chem. Soc.*, 1950, **72**, 3084) that 5-methyl- and 5 : 6-dimethyl-benziminazole showed significant vitamin B_{12}-like growth-activity in the rat test, whilst 2 : 5-dimethylbenziminazole showed growth-depressant or -inhibitor properties. The synthesis of some 2-methyl- and 2 : 5-dimethyl-1-glycosyl-benziminazoles was, therefore, included in the present investigation.

The preparation of 5-chloro-1-β-D-glucopyranosylbenziminazole (cf. VI; R = glucosyl, R′ = H) was effected essentially by methods previously developed in this laboratory (Mamalis, Petrow, and Sturgeon, *J. Pharm. Pharmacol.*, 1950, **2**, 491, 503, 512). Condensation of 4-chloro-2-nitroaniline with D-glucose in ethanol in the presence of ammonium chloride (Kuhn and Strobële, *Ber.*, 1937, **70**, 773) furnished a mixture of *N*-D-glucosyl derivatives (cf. III; R = glucosyl) from which only one isomer was obtained in a state of purity. Acetylation of the crude mixture, however, followed by fractionation, yielded 4-chloro-1-(tetra-acetyl D-glucosyl)-2-nitroaniline I and II. Reduction of either isomer, followed by treatment with ethyl orthoformate, furnished 5-chloro-1-(β-tetra-acetyl *D*-glucosyl)benziminazole, from which the corresponding 5-chloro-1-β-D-glucopyranosylbenziminazole (cf. VI; R′ = H, R = β-D-glucopyranosyl) was obtained by ethanolysis in the presence of a catalytic amount of sodium ethoxide. Attempts to confirm the β-configuration of the glycosidic centre in the last compound by its alternative synthesis from the silver derivative of 5-chlorobenziminazole (cf. VII; R′ = H) and α-acetobromoglucose proved uniformly unsuccessful. The constitution assigned to the glycosidic centre follows, however, from the detailed studies previously referred to (Mamalis *et al.*, *loc. cit.*).

Attempts to employ D-xylose and L-arabinose as the sugar component in the foregoing synthesis proved disappointing. The corresponding *o*-nitroaniline "pentosides" I and II were readily obtained in each instance. Reduction of the triacetyl xylosides, followed by reaction with ethyl orthoformate, gave what was presumably 5-chloro-1-(triacetyl D-xylosyl)-benziminazole, isolated as the picrate, but the yield was too low to permit satisfactory identification of the product. Complete failure attended attempts to convert the triacetyl L-arabinosyl derivatives into the corresponding glycosylbenziminazole. 4-Iodo-2-nitroaniline condensed with D-glucose, but acetylation of the crude product, followed by fractionation, gave only a single 4-iodo-2-nitro-1-(tetra-acetyl D-glycosyl)aniline, from which a benziminazole could not be obtained.

The foregoing synthesis could not be extended to the preparation of 5 : 6-dichloro-1-glycosyl benziminazoles as the intermediate 4 : 5-dichloro-1-glycosyl-*o*-nitroanilines could not be prepared by Kuhn and Ströbele's method (*loc. cit.*). Condensation of the silver derivative

of 5 : 6-dichloro-2-methylbenziminazole (cf. VII; R′ = Me) with α-acetobromogluoose likewise proved unsuccessful, the unchanged dichloro-compound being recovered in high yield. Attention was, therefore, directed to the preparation of the corresponding 1-deoxyglycosides, which were readily obtained from the appropriate 4 : 5-dichloro-*N*-glycityl-2-nitroanilines (cf. III). The preparation of the latter compounds was achieved by the method of Kuhn *et al.* (*loc. cit.*). Reaction of 1 : 2-dichloro-4 : 5-dinitrobenzene with D-ribosamine, L-arabosamine, and D-glucosamine furnished the 4 : 5-dichloro-*N*-glycityl-2-nitroanilines (cf. III) (Weygand *et al.*, *loc. cit.*). Catalytic reduction of these compounds, followed by treatment with formic acid in 4N-hydrochloric acid (Philips, *J.*, 1929, 1143), gave the 1-D-ribityl, 1-L-arabityl, and 1-D-sorbityl derivatives of 5 : 6-dichlorobenziminazole (cf. VI; R′ = H). The last compound has recently been described by Holly, Peel, Cahill, and Folkers (*J. Amer. Chem. Soc.*, 1951, **73**, 332) in connection with studies on carcinolytic compounds. By employing acetic acid in place of formic acid in the above condensations, the 1-D-ribityl, 1-L-arabityl, and 1-D-sorbityl derivatives of 5 : 6-dichloro-2-methylbenziminazole (cf. VI; R′ = Me) were readily obtained.

The preparation of 1-glycosyl-2-methylbenziminazoles has not hitherto been recorded in the literature, but has now been effected by extension of the methods developed by Mamalis *et al.* (*loc. cit.*). Thus reaction of *N*-(tetra-acetyl D-glucopyranosyl)-*o*-phenylenediamine (cf. IV), which was obtained crystalline for the first time, with ethyl orthoacetate, furnished the acetimidate (V; R = tetra-acetyl D-glucopyranosyl) in excellent yield. Dilute hydrochloric acid then effected ring closure to give 2-methyl-1-(β-tetra-acetyl D-glucopyranosyl)-benziminazole (cf. VI; R′ = Me). The corresponding 2 : 5-dimethyl-1-β-(tetra-acetyl D-glucopyranosyl) compound, converted by dilute hydrochloric acid into the hydrochloride of the 1-(β-D-glucopyranosyl) compound, was prepared in the same way, as well as 2-methyl- and 2 : 5-dimethyl-1-(β-triacetyl D-xylopyranosyl)benziminazole.

Experimental.

M. p.s are uncorrected.

4-Chloro-N-D-glucosyl-2-nitroanilins.—4-Chloro-2-nitroaniline (71 g.), glucose (30 g.), and ammonium chloride (5 g.) were heated under reflux in absolute ethanol (400 ml.) for 6 hours. After removal of part of the ethanol by distillation, the solution was poured through a column of alumina (B.D.H.; 1¾ × 15″), and excess of 4-chloro-2-nitroaniline was washed out with benzene. Elution with ethanol, followed by concentration of the eluate, gave *4-chloro-N-D-glucosyl-2-nitroaniline* as yellow needles (from acetone–ethanol), m. p. 185°, $[\alpha]_D^{24}$ +7·96° (*c*, 2·194 in pyridine) (Found: C, 43·5; H, 4·6; N, 8·9. $C_{12}H_{15}O_8N_2Cl$ requires C, 43·0; H, 4·4; N, 8·3%).

4-Chloro-2-nitro-1-(tetra-acetyl D-glucosyl)aniline I *and* II.—The crude mixture of glucosyl derivatives (12 g.), obtained as described above, was dissolved in pyridine (90 ml.) and treated with acetic anhydride (100 ml.) at room temperature. After 24 hours excess of anhydride was destroyed by addition of ethanol, and the solution concentrated under reduced pressure to a small bulk. Crystallisation of the syrupy residue from ethyl acetate–light petroleum (b. p. 40—60°) gave *4-chloro-2-nitro-1-(tetra-acetyl D-glucosyl)aniline* I, yellow needles, m. p. 150°, $[\alpha]_D^{24}$ −63·4° (*c*, 1·35 in chloroform) (Found: C, 48·3; H, 4·5; N, 5·7. $C_{20}H_{23}O_{11}N_2Cl$ requires C, 47·7; H, 4·6; N, 5·6). Concentration of the mother-liquors gave the *isomer* II, yellow needles (from ethanol), m. p. 126°, $[\alpha]_D^{24}$ +115·8° (*c*, 2·07 in chloroform) (Found: C, 47·4; H, 4·5; N, 6·4%).

4-Chloro-N-D-xylosyl-2-nitroaniline crystallised from aqueous ethanol in yellow needles, m. p. 180°, $[\alpha]_D^{23}$ −59·6° (*c*, 1·016 in pyridine) (Found: C, 42·9; H, 4·4; N, 9·7. $C_{11}H_{13}O_7N_2Cl$ requires C, 43·3; H, 4·2; N, 9·1%).

4-Chloro-2-nitro-N-(triacetyl D-xylosyl)aniline I crystallised from ethanol in yellow needles, m. p. 162°, $[\alpha]_D^{21}$ −90·1° (*c*, 1·118 in chloroform) (Found: C, 47·6; H, 4·4; N, 6·8. $C_{17}H_{19}O_{10}N_2Cl$ requires C, 47·3; H, 4·4; N, 6·5%). The *isomer* II separated from ethanol in yellow needles, m. p. 117°, $[\alpha]_D^{23}$ +96·7° (*c*, 0·716 in chloroform) (Found: C, 47·0; H, 4·3; N, 6·3%).

N-L-Arabinosyl-4-chloro-2-nitroanilins formed yellow needles (from aqueous ethanol), m. p. 110° (Found: C, 42·6; H, 4·4; N, 9·6%).

4-Chloro-2-nitro-N-(triacetyl L-arabinosyl)aniline I separated from aqueous ethanol in yellow needles, m. p. 194°, $[\alpha]_D^{21}$ +150·9° (*c*, 1·26 in chloroform) (Found: C, 47·8; H, 3·9; N, 6·5%). The *enantiomer* II formed yellow needles [from ethyl acetate–light petroleum (b. p. 60—80°)], m. p. 117°, $[\alpha]_D^{21}$ +10·5° (*c*, 0·894 in chloroform) (Found: N, 6·1%).

N-D-Glucosyl-4-iodo-2-nitroanilins crystallised from ethanol in yellow plates, m. p. 136° (decomp.), $[\alpha]_D^{23}$ +8·6° (*c*, 1·19 in pyridine) (Found: C, 33·0; H, 3·7; N, 6·2. $C_{12}H_{15}O_7N_2I$ requires C, 33·8; H, 3·5; N, 6·6%). The *tetra-acetyl* derivative formed yellow plates (from ethanol), m. p. 135°, $[\alpha]_D^{20}$ −69·8° (*c*, 0·866 in pyridine) (Found: C, 39·9; H, 4·1; N, 4·9. $C_{20}H_{23}O_{11}N_2I$ requires C, 40·0; H, 3·8; N, 4·7%).

5-Chloro-1-(β-tetra-acetyl D-glucosyl)benziminazole.—4-Chloro-2-nitro-1-(tetra-acetyl D-glucosyl)aniline I or II (7 g.) was reduced catalytically in ethanolic solution (50 ml.) in the presence of 5% palladised charcoal (3 g.), to the corresponding diamine which was heated with ethyl orthoformate (30 ml.) for 3 hours. Excess of ortho-ester was removed by distillation under reduced pressure, and ring-closure effected by heating with N/40-aqueous-alcoholic hydrochloric acid for 1 hour. The product yielded

5-chloro-1-(β-tetra-acetyl D-*glucopyranosyl)benziminazole picrate*, yellow needles (from ethanol), m. p. 173° (Found: C, 45·7; H, 3·6; N, 9·4. $C_{31}H_{33}O_{9}N_{9}Cl,C_{6}H_{3}O_{7}N_{3}$ requires C, 45·2; H, 3·6; N, 9·8%), which was decomposed by percolation of its chloroform solution through a column of alumina. The *5-chloro-1-(β-tetra-acetyl* D-*glucosyl)benziminazole* so obtained formed needles [from ethyl acetate–light petroleum (b. p. 60—80°)], m. p. 156°, $[\alpha]_{D}^{23}$ −39·0° (*c*, 0·95 in chloroform) (Found: C, 52·3; H, 4·7; N, 6·0. $C_{21}H_{23}O_{8}N_{2}Cl$ requires C, 52·2; H, 4·7; N, 5·8%). Deacetylation with ethanol containing a trace of sodium ethoxide furnished *5-chloro-1-β-*D-*glucopyranosylbenziminazole*, rosettes of needles (from aqueous ethanol), m. p. 247°, $[\alpha]_{D}^{19}$ −24·6° (*c*, 1·644 in pyridine) (Found: C, 50·0; H, 4·7; N, 8·7. $C_{13}H_{15}O_{6}N_{2}Cl$ requires C, 49·6; H, 4·7; N, 8·8%).

5 : 6-Dichloro-2-methylbenziminazole.—4 : 5-Dichloro-2-nitroaniline (7 g.) in ethanol (70 ml.) was catalytically hydrogenated in the presence of 5% palladised charcoal (3 g.) to the corresponding diamine. After filtration and removal of the ethanol by distillation, acetic acid (5 ml.) and 4N-hydrochloric acid (40 ml.) were added and the mixture was heated under reflux for 40 minutes. *5 : 6-Dichloro-2-methylbenziminazole*, isolated in the usual way, formed pale yellow needles (from aqueous ethanol), m. p. 249° (Found: C, 47·8; H, 3·0; N, 13·7. $C_{8}H_{6}N_{2}Cl_{2}$ requires C, 47·7; H, 3·0; N, 13·9%). The *picrate* crystallised from ethanol in yellow needles, m. p. 252° (decomp.) (Found: N, 16·6. $C_{8}H_{6}N_{2}Cl_{2},C_{6}H_{3}O_{7}N_{3}$ requires N, 16·3%).

*5 : 6-Dichloro-1-*D-*sorbitylbenziminazole.*—4 : 5-Dichloro-2-nitro-*N*-D-sorbitylaniline (1 g.) in ethanol (30 ml.) was catalytically hydrogenated in the presence of 5% palladised charcoal (1 g.) to the corresponding diamine. After filtration and removal of the alcohol by distillation, the residue was treated with 4N-hydrochloric acid (8 ml.) and formic acid (0·5 ml.). The mixture was heated on the steam-bath for 20 minutes. It was then filtered, cooled, and basified with aqueous ammonia. The product was collected and crystallised from aqueous ethanol, yielding *5 : 6-dichloro-1-*D-*sorbitylbenziminazole*, needles, m. p. 206° with a transition at 147° (Found: C, 43·6; H, 5·0; N, 7·8. Calc. for $C_{13}H_{16}O_{4}N_{2}Cl_{2}$: C, 44·4; H, 4·6; N, 7·9. Holly *et al.* (*loc. cit.*) give m. p. 198—200° with a transition at 147°.

*5 : 6-Dichloro-1-*L-*arabitylbenziminazole* formed needles (from aqueous ethanol), m. p. 191° (Found: C, 45·5; H, 5·0; N, 9·2. $C_{12}H_{14}O_{4}N_{2}Cl_{2}$ requires C, 44·9; H, 4·4; N, 8·7%), and *5 : 6-dichloro-1-*D-*ribitylbenziminazole* crystallised from aqueous ethanol in needles, m. p. 187° (transition at 143°) (Found: C, 45·3, 45·1; H, 5·3, 5·2; N, 8·5%).

*5 : 6-Dichloro-2-methyl-1-*D-*sorbitylbenziminazole* formed needles (from aqueous ethanol), m. p. 225° (Found: C, 46·9; H, 5·0; N, 7·5. $C_{14}H_{18}O_{4}N_{2}Cl_{2}$ requires C, 46·0; H, 4·9; N, 7·6%). *1-*L-*Arabityl-5 : 6-dichloro-2-methylbenziminazole* separated from aqueous ethanol in needles, m. p. 247° (Found: C, 46·7; H, 5·4; N, 8·4. $C_{13}H_{16}O_{4}N_{2}Cl_{2}$ requires C, 46·5; H, 4·7; N, 8·4%), and *5 : 6-dichloro-2-methyl-1-*D-*ribitylbenziminazole* formed needles (from aqueous ethanol), m. p. 207° (Found: C, 46·7; H, 4·8; N, 8·3%).

*2-Methyl-1-(β-tetra-acetyl-*D-*glucopyranosyl)benziminazole.*—*o*-Nitro-*N*-(tetra-acetyl D-glucopyranosyl)aniline (15 g.) in ethanol (100 ml.) was catalytically hydrogenated in the presence of 5% palladised charcoal (5 g.) to give N-(*tetra-acetyl* D-*glucopyranosyl*)-*o*-*phenylenediamine*, needles (from ethanol), m. p. 182°, $[\alpha]_{D}^{19}$ −89·5° (*c*, 0·668 in chloroform) (Found: C, 54·2; H, 6·0; N, 6·8. $C_{20}H_{28}O_{9}N_{2}$ requires C, 54·7; H, 5·9; N, 6·4%).

This diamine was heated with ethyl orthoacetate (30 ml.) on the steam-bath for 2 hours, after which excess of ortho-ester was removed by distillation under reduced pressure. The residue, on crystallisation from alcohol–light petroleum (b. p. 40—60°), gave *o*-(*1-ethoxyethylideneamino*)-N-(*tetra-acetyl* D-*glucopyranosyl*)*aniline*, needles, m. p. 189°, $[\alpha]_{D}^{23}$ −91·7° (*c*, 2·864 in chloroform) (Found: C, 57·0; H, 6·3; N, 5·8. $C_{24}H_{32}O_{10}N_{2}$ requires C, 56·6; H, 6·1; N, 5·5%).

This compound (7 g.) was treated with a mixture of ethanol (80 ml.), 0·1N-hydrochloric acid (40 ml.), and water (40 ml.) under reflux for 1 hour on the steam-bath. After removal of part of the ethanol the product crystallised on cooling. Crystallisation from ethanol–light petroleum gave *2-methyl-1-(β-tetra-acetyl* D-*glucopyranosyl)benziminazole*, needles, m. p. 202°, $[\alpha]_{D}^{23}$ −30·2° (*c*, 0·109 in chloroform) (Found: C, 55·8; H, 5·4; N, 6·6. $C_{21}H_{24}O_{9}N_{2}$ requires C, 57·1; H, 5·6; N, 6·1%).

2 : 5-Dimethyl-1-(β-tetra-acetyl D-*glucopyranosyl)benziminazole.*—4-Methyl-3-nitro-*N*-(tetra-acetyl D-glucopyranosyl)aniline (14 g.) in ethanol (100 ml.) was catalytically reduced in the presence of 5% palladised charcoal to the corresponding diamine, which was not isolated but was treated with ethyl orthoacetate (30 ml.). The mixture was heated on the steam-bath for 3 hours. Removal of excess of ortho-ester by vacuum-distillation gave the *ethoxyethylidene* compound, needles [from ethanol–light petroleum (b. p. 40—60°)], m. p. 138°, $[\alpha]_{D}^{23}$ −85·7° (*c*, 3·018 in chloroform) (Found: C, 57·5; H, 6·5; N, 5·6. $C_{23}H_{34}O_{10}N_{2}$ requires C, 57·4; H, 6·5; N, 5·4%).

The foregoing product (7 g.) was heated under reflux with ethanol (80 ml.), 0·1N-hydrochloric acid (40 ml.), and water (40 ml.) for 1 hour, giving *2 : 5-dimethyl-1-(β-tetra-acetyl* D-*glucopyranosyl)-benziminazole*, needles (from ethanol), m. p. 220°, $[\alpha]_{D}^{23}$ −43·4° (*c*, 1·538 in chloroform) (Found: C, 58·2; H, 6·0; N, 6·3. $C_{23}H_{28}O_{9}N_{2}$ requires C, 57·9; H, 5·9; N, 5·9%).

Hydrolysis with 6N-hydrochloric acid for 1 hour under reflux then gave *2 : 5-dimethyl-1-(β-*D-*glucopyranosyl)benziminazole hydrochloride*, needles (from aqueous acetone), m. p. 236° (decomp.), $[\alpha]_{D}^{23}$ +20° (*c*, 1·262 in water) (Found: C, 52·2; H, 6·1; N, 8·1. $C_{15}H_{21}O_{6}N_{2}Cl$ requires C, 52·0; H, 6·6; N, 7·9%).

2-Methyl-1-(β-triacetyl D-*xylopyranosyl)benziminazole.*—Reduction of *o*-nitro-*N*-(triacetyl D-xylopyranosyl)aniline gave the corresponding *diamine*, white plates (from ethanol), m. p. 179°, $[\alpha]_{D}^{23}$ −50° (*c*, 2·954 in chloroform) (Found: C, 54·6; H, 5·6; N, 8·3. $C_{17}H_{22}O_{7}N_{2}$ requires C, 55·7; H, 6·0; N, 7·6%). The *ethoxyethylidene* compound crystallised from ethanol in needles, m. p. 139°, $[\alpha]_{D}^{19}$ −62·1° (*c*, 2·872 in chloroform) (Found: C, 57·7; H, 6·4; N, 6·5. $C_{19}H_{26}O_{8}N_{2}$ requires C, 57·8; H, 6·4; N, 6·4%). Cyclisation then gave *2-methyl-1-(β-triacetyl* D-*xylopyranosyl)benziminzole*, needles (from

aqueous ethanol), m. p. 226° $[\alpha]_D^{22}$ −76·3° (*c*, 1·16 in chloroform) (Found: C, 59·2; H, 5·5; N, 7·2. $C_{19}H_{23}O_7N_3$ requires C, 58·4; H, 5·6; N, 7·2%).

2 : 5-*Dimethyl*-1-(*β-triacetyl* D-*xylopyranosyl*)*benziminazole* formed needles (from ethanol), m. p. 258°, $[\alpha]_D^{22}$ −93·9° (*c*, 1·026 in chloroform) (Found: C, 59·4; H, 6·0; N, 6·9. $C_{22}H_{24}O_7N_2$ requires C, 59·4; H, 5·9; N, 6·9%).

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641. *The Preparation of α-Aryl Ethers of* iso*Butane*-1 : 2 : 3-*triol.*

By WILLIAM BRADLEY, JAMES FORREST, and OLIVER STEPHENSON.

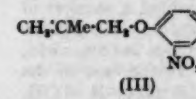
The recognition of muscle-relaxing properties amongst α-aryl ethers of glycerol has led to a study of the means of preparing analogous ethers of its β-methyl derivative (*iso*butane-1 : 2 : 3-triol).

The ethers can be prepared by forming the 2-methylallyl ethers of phenols and oxidising these by means of peracetic or performic acid. The course of the oxidation is discussed. The same ethers of *iso*butane-1 : 2 : 3-triol are obtained in better yield and more conveniently by condensing phenols with 1 : 2-epoxy-3-hydroxy*iso*butane (β-methylglycidol) in the presence of pyridine. A third method of preparation consists in oxidising 2-methylallyl chloride with peracetic acid to form 3-chloro*iso*butane-1 : 2-diol and condensing this with phenols. The three methods of preparation yield identical ethers of *iso*butane-1 : 2 : 3-triol.

THE investigation of the α-aryl ethers of glycerol already reported (*J.*, 1951, 1589) has been extended to include the preparation of analogous ethers of *iso*butane-1 : 2 : 3-triol. The ready availability of 2-methylallyl chloride (I; R = Cl) enabled a series of aryl 2-methylallyl ethers (I; R = OAr) to be obtained, and from these the ethers (II; R = OAr, R′ = OH) by oxidation.

(I) $CH_2{:}CMe{\cdot}CH_2R$ $\qquad$ $R{\cdot}CH_2{\cdot}CMe(OH){\cdot}CH_2R'$ (II)

Several authors (Bortz, Miller, and Adams, *J. Amer. Chem. Soc.*, 1935, **57**, 371; Mauthner, *J. pr. Chem.*, 1937, **148**, 95) have described the formation of 2-methylallyl ethers of phenols by heating phenols with 2-methylallyl chloride and aqueous-alcoholic sodium hydroxide or a suspension of anhydrous potassium carbonate in dry acetone. We have employed the same conditions in preparing the 2-methylallyl ethers of *m*- and *p*-nitrophenol, 4-chloro-3-methylphenol, butyl *m*- and *p*-hydroxybenzoate, butyl 4-hydroxy-3-nitrobenzoate, and *p*-hydroxybenzoic acid. The more acidic phenols reacted slowly and in these cases it was found advantageous to employ 2-methylallyl iodide, prepared *in situ* from 2-methylallyl chloride and sodium iodide. Care was required in purifying the 2-methylallyl ethers because of their tendency to rearrange during distillation (Bortz, Miller, and Adams, *loc. cit.*), except that butyl 4-2′-methylallyloxy-3-nitrobenzoate (III), unlike the corresponding allyl ether, distilled almost unchanged at 180° under reduced pressure.



(III)

The oxidation of the 2-methylallyl ethers was effected by means of peracetic acid prepared by warming 100-vol. hydrogen peroxide with glacial acetic acid at 80° for an hour. Oxidation occurred readily at 60° and cooling was required to prevent undue rise in temperature. The oxidation products consisted of the methylglycerol ethers (II; R = OAr, R′ = OH) together with *O*-acetates of undetermined constitution. After separation of the product from the medium, and its hydrolysis with either aqueous-alcoholic sulphuric acid or a suspension of anhydrous potassium carbonate in alcohol (Fischer, *Ber.*, 1920, **53**, 1634), the whole of the oxidation product was obtained in the form of the methylglycerol ether (II; R = OAr, R′ = OH). The yields of these ethers varied greatly (from 6 to 68%) with the nature of the nuclear substituents in the aryl 2-methylallyl ether oxidised. The use of performic acid (Swern, Billen, Findley, and Scanlar, *J. Amer. Chem. Soc.*, 1945, **67**, 1786) afforded greatly improved yields in the case of the *m*-methyl (25%) and 3 : 4-dimethyl (50%) derivatives of 2-methylallyl phenyl ether.

When the oxidation was carried out by means of peracetic acid the methylglycerol ethers (II; R = OAr, R′ = OH) could usually be readily obtained crystalline. The mother-liquors contained the *O*-acetate of the methylglycerol ether, the amounts of which could be estimated by hydrolysis with aqueous-alcoholic sulphuric acid to the methylglycerol ether. It was thus found, in one experiment, that when 2-methylallyl phenyl ether was oxidised the ratio of methylglycerol ether to its *O*-acetate was 3·1 : 1. In a similar experiment with 2-methylallyl *p*-tolyl ether the ratio was 1·2—1·3 : 1, and in several experiments with *p*-chlorophenyl 2-methylallyl ether the ratio varied from 0·8 : 1 to 2·0 : 1 according to the conditions.

(IV) $CH_2\langle O \rangle CMe\cdot CH_2\cdot OR$ $ArO\cdot CH_2\cdot CMe(OH)\cdot CH_2\cdot NR_2$ (V)

When the oxidation with peracetic acid was carried out for a shorter time and at a higher temperature (80°) it was often possible to isolate the epoxide (IV; R = Ar) in good yield. Epoxides were readily prepared from the 2-methylallyl ethers of phenol, *o*-cresol, *p*-cresol, and *p*-chlorophenol, and their occurrence in the oxidation product supports the conclusion of Swern *et al.* (*loc. cit.*) that the appearance of epoxides in oxidation processes is not limited to reactions in non-hydroxylic solvents. The persistence of an epoxide depends upon the ease of its reaction with the medium in which it is formed. In this connection it may be mentioned that the epoxides derived from the 2-methylallyl ethers of phenols are notably more stable towards acid hydrolysis than the corresponding epoxides of allyl ethers.

The epoxides isolated after oxidations with peracetic acid reacted with glacial acetic acid or with a solution of peracetic acid in acetic acid to form the methylglycerol ethers (II; R = OAr, R′ = OH) and the related *O*-acetates in approximately the same proportions as those in which these compounds occurred in the product of oxidising the 2-methylallyl ethers. This supports the view that the first product of the oxidation of an aryl 2-methylallyl ether is the related epoxide, which then reacts with the medium to form the methylglycerol ether (II; R = OAr, R′ = OH) and its *O*-acetate.

Another factor affecting the proportion of the *O*-acetate found in the oxidation products is the esterification of acetic acid by the methylglycerol ether formed at an earlier stage. This was shown by experiments with 3-*p*-chlorophenoxy*iso*butane-1 : 2-diol. The importance of the esterification factor is considerable when the oxidation time is prolonged and the proportion of water in the medium is small. The product is probably a 1-acetoxy-3-aryloxy*iso*butan-2-ol (II; R = OAr, R′ = OAc), in view of the greater ease of acylation of primary than of tertiary alcohols.

Although the oxidation of aryl 2-methylallyl ethers sometimes affords low yields of the corresponding methylglycerol ethers, the method of preparation is of value because the constitution of the products follows from their mode of preparation.

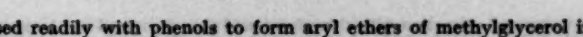
The use of potassium permanganate in acetone as an oxidant was studied in the case of *p*-chlorophenyl 2-methylallyl ether. The corresponding ether of methylglycerol was obtained but the yield was much inferior to that of the preparation by use of peracetic acid.

It was later found that 2-methylallyl chloride was readily oxidised to 3-chloro*iso*butane-1 : 2-diol (II; R = Cl, R′ = OH) by peracetic acid. This intermediate enabled a number of aryl ethers of methylglycerol to be prepared directly in good yield. Reaction with *p*-iodophenol gave 3-*p*-iodophenoxy*iso*butane-1 : 2-diol (II; R = OH, R′ = $O\cdot C_6H_4I$-*p*) in 68% yield, and the yields obtained with other derivatives of phenol were 33—78%. In the case of the *m*-methyl and 3 : 5-dimethyl derivatives of 3-phenoxy*iso*butane-1 : 2-diol (II; R = OH, R′ = OPh), direct comparison showed that the methylglycerol ethers obtained by the use of 3-chloro*iso*butane-1 : 2-diol were identical with the ethers derived by oxidising the 2-methylallyl ethers of the corresponding phenols.

The oxidation of 2-methylallyl chloride by means of peracetic acid yields in the first instance a mixture of (II; R = Cl, R′ = OH) and an *O*-acetate. 3-Chloro*iso*butane-1 : 2-diol (II; R = Cl, R′ = OH) can be prepared in good yield by heating the mixture with aqueous-alcoholic sulphuric acid. A suspension of potassium carbonate in alcohol may also be used, but *iso*butane-1 : 2 : 3-triol 1-ethyl ether (II; R = OEt, R′ = OH) then appears as a by-product. For most purposes the mixture of (II; R = Cl, R′ = OH) and its *O*-acetate could be employed, the condensation products with phenols being obtained free from esters by ester-exchange with the solvent during the reaction.

A convenient procedure has been devised to prepare β-methylglycidol (IV; R = H) from 3-chloro*iso*butane-1 : 2-diol or from the mixture of this with its *O*-acetate following Rider and Hill's method (*J. Amer. Chem. Soc.*, 1930, **52**, 1521). In the presence of catalysts (IV;

R = H) condensed readily with phenols to form aryl ethers of methylglycerol in good yield (*m*-nitrophenol, 10%; 7 others, 55—70%). The products obtained by condensing β-methylglycidol with phenol, *m*-cresol, *p*-cresol, 4-chloro-3-methylphenol, and *m*-nitrophenol were shown to be identical with the corresponding 3-aryloxy*iso*butane-1 : 2-diols (II; R = OAr, R′ = OH) obtained by the oxidation of the 2-methylallyl ethers of phenols. The structure of the products obtained by condensing β-methylglycidol with phenols indicates that in this reaction it is the terminal carbon atom of the oxide ring which is reactive towards phenols or phenoxide ions.



By analogy, the *O*-acetates derived by the action of acetic acid on the epoxides (IV; R = Ar) are most probably 1-acetoxy-3-aryloxy*iso*butan-2-ols (II; R = OAr, R′ = OAc), and the same constitution must be assigned to the *O*-acetates which occur in the products of the oxidation of aryl 2-methylallyl ethers by means of peracetic acid, because these also are derived from the epoxides (IV; R = Ar). Further, for the same reason the *O*-acetate which accompanies the 3-chloro*iso*butane-1 : 2-diol prepared by the action of peracetic acid on 2-methylallyl chloride is doubtless 1-acetoxy-3-chloro*iso*butan-2-ol (II; R = Cl, R′ = OAc).

In experiments designed to estimate the yields of epoxides, β-methylglycerol ethers, and *O*-acetates resulting from the oxidation of aryl 2-methylallyl ethers, it was found convenient in several instances to add a secondary amine such as piperidine or diethylamine to the isolated crude oxidation product with the object of converting the epoxide constituent into an adduct with the amine. The reaction occurred readily in all the cases encountered. The products were probably 1-aryloxy-3-piperidino*iso*butan-2-ols (V; NR_2 = piperidino) or the corresponding 3-diethylamino-compounds (V; R = Et).

The product obtained by oxidising 2-methylallyl phenyl ether with peracetic acid and combining the derived epoxide with piperidine was therefore 1-phenoxy-3-piperidino*iso*butane-2-ol (V; Ar = Ph, NR_2 = piperidino). Analogously, the products obtained by oxidising the 2-methylallyl ethers of *o*-cresol, *p*-cresol, and *p*-chlorophenol by means of peracetic acid and combining the derived epoxides with diethylamine were (V; R = Et, Ar = *o*-C_6H_4Me, *p*-C_6H_4Me, or *p*-C_6H_4Cl).

Experimental.

3-m-*Tolyloxyisobutane*-1 : 2-*diol*.—(1*a*) 2-Methylallyl *m*-tolyl ether (50 g.) was added at 40° to a solution of hydrogen peroxide (100-vol.; 75 g.) in acetic acid (240 c.c.), which had been previously warmed to 80° for an hour and then cooled. When the mixture was warmed to 60° the ether dissolved, forming a solution which became orange-red. This was heated at 70° for an hour and then poured into water (2 vols.) and extracted by means of chloroform. The extract was washed with dilute sodium hydroxide solution then with water, and the solvent was removed by distillation. The residual reddish oil was dissolved in a mixture of water (50 c.c.) and alcohol (100 c.c.) containing concentrated sulphuric acid (2 c.c.), and the solution was heated under reflux for 1·5 hours. Water was added, and the product extracted by means of chloroform. Evaporation of the extract gave the *diol* as a solid which, after crystallisation from ether–light petroleum, was obtained in colourless crystals, m. p. 71—72° (3·7 g.) (Found: C, 67·0; H, 7·8. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%).

(1*b*) The same product was obtained in better yield by suspending 2-methylallyl *m*-tolyl ether (40 g.) in formic acid (125 c.c.), cooling the suspension in ice-water, and stirring it vigorously while hydrogen peroxide (100-vol.; 30 c.c.) was added dropwise. The deep red-brown product (18 g.) so obtained, crystallised from ether–light petroleum, had m. p. 71—72°; the final yield was 10·2 g.

(2) A mixture of *m*-cresol (10·8 g.), β-methylglycidol (8·8 g.), and pyridine (0·1 g.) was heated at 90° for 2 hours. The resulting brown product was added to water and the mixture then extracted by means of chloroform (150 c.c.). The extract was washed twice with water, then concentrated by distilling a portion of the solvent, and finally mixed with light petroleum. On cooling, needles, m. p. 70—72°, separated. The m. p. was raised to 71—72° after three recrystallisation from ether–light petroleum. The product (11·5 g.) was identical with that obtained by the oxidation of 2-methylallyl *m*-tolyl ether. The same compound was formed when *m*-cresol was condensed with 1-chloro*iso*butane-1 : 2-diol.

3-o-*Tolyloxyisobutane*-1 : 2-*diol*.—This was prepared similarly both (i) by oxidising 2-methylallyl *o*-tolyl ether and (ii) by condensing *o*-cresol with β-methylglycidol. (i) 2-Methylallyl *o*-tolyl ether (121·5 g.) was added in one portion to peracetic acid prepared from hydrogen peroxide (100-vol; 171 g.) and acetic acid (420 c.c.). When heated and shaken, the mixture became homogeneous at 55°, and then the temperature rose sharply to 80°. After 5 minutes at this temperature the deep red solution was cooled rapidly and then poured into water. The oil which separated was taken up in chloroform and fractionated to give: (*a*) mainly unchanged 2-methylallyl *o*-tolyl ether, b. p. 54°/0·5 mm. (48 g.); (*b*) a fraction, b. p. 54—100° (mainly 76—80°)/0·5 mm., 46·5 g.; (*c*) a fraction, b. p. 140—150°/0·5 mm. Redistillation of fraction (*b*) gave 1 : 2-epoxy-3-*o*-tolyloxy*iso*butane, b. p. 78—80°/0·5 mm. (26·1 g.)

In a similar preparation, in which 2-methylallyl *o*-tolyl ether was oxidised by means of peracetic acid (prepared from 2·1 mols. of hydrogen peroxide) at 65—70° for 2·5 hours, the product was isolated

by addition of water and extraction with chloroform, and then recovered and hydrolysed by heating it with aqueous-alcoholic sulphuric acid. Isolation by means of chloroform and distillation gave 3-*o*-*tolyloxyisobutane*-1 : 2-*diol*, b. p. 124—126°/0·05 mm. (30%) (Found: C, 67·1; H, 7·9. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%).

(ii) The same product was obtained in 55% yield by condensing *o*-cresol (1·05 mols.) with β-methylglycidol (1·0 mol.) for 3·5 hours at 90—95° in the presence of pyridine. It was also prepared (yield, 63%) by condensing *o*-cresol (1 mol.) with 3-chloro*iso*butane-1 : 2-diol (1·5 mols.) in alcohol containing potassium carbonate.

1-*Diethylamino*-3-*o*-*tolyloxyisobutan*-2-*ol*.—This *alcohol* resulted when 1 : 2-epoxy-3-*o*-tolyloxy*iso*butane was mixed with diethylamine in slight excess. Distillation gave a fraction, b. p. 144—145°/0·5 mm. (Found: C, 71·4; H, 10·0; N, 5·5. $C_{15}H_{25}O_3N$ requires C, 71·7; H, 10·0; N, 5·6%).

3-(3 : 5-*Dimethylphenoxy*)iso*butane*-1 : 2-*diol*.—3 : 5-Dimethylphenyl 2-methylallyl ether (44 g.) was added at 40°, with shaking, to a solution of peracetic acid prepared from acetic acid (180 c.c.) and hydrogen peroxide (100-vol.; 57 g.). Treatment as described for 3-*m*-tolyloxy*iso*butane-1 : 2-diol (1*a*) gave almost pure *diol* (3 g.), m. p. 74° (Found: C, 68·6; H, 8·5. $C_{15}H_{14}O_3$ requires C, 68·6; H, 8·6%). The same percentage yield was obtained when 3 : 5-dimethylphenyl 2-methylallyl ether (22 g.) was oxidised at 5° by means of a solution of 100-vol. hydrogen peroxide (11·3 g.) in formic acid (125 c.c.).

3-(3 : 4-*Dimethylphenoxy*)iso*butane*-1 : 2-*diol*.—3 : 4-Dimethylphenyl 2-methylallyl ether (80 g.) was heated for an hour at 60—70° with peracetic acid prepared from acetic acid (360 c.c.) and hydrogen peroxide (100-vol.; 114 g.). The product was heated for 30 minutes at 90—95° with a solution containing concentrated sulphuric acid (2 c.c.) in a mixture of water (40 c.c.) and methanol (100 c.c.). The hydrolysed product, recrystallised from ether, afforded white needles of the *diol* (20 g.), m. p. 96° (Found: C, 68·4; H, 8·2. $C_{12}H_{18}O_3$ requires C, 68·6; H, 8·6%).

The yield was considerably improved when performic acid was used instead of peracetic acid. 3 : 4-Dimethylphenyl 2-methylallyl ether (37 g.) was vigorously stirred for an hour with a solution of hydrogen peroxide (100-vol.; 30 c.c.) in formic acid (125 c.c.), the temperature being kept below 30°. All the ether had then dissolved. After 30 minutes' more stirring at room temperature, the product was isolated and hydrolysed with aqueous-methanolic sulphuric acid as in the preceding preparation. The yield of the pure methylglycerol ether, m. p. 96°, was 20·2 g.

3-*Phenoxyisobutane*-1 : 2-*diol*.—(1*a*) To a solution of peracetic acid, prepared from acetic acid and 2·1 mols. of hydrogen peroxide, was added 2-methylallyl phenyl ether (1 mol.). The mixture was kept at 65—70° for 2—3 hours and then the product was isolated and heated with aqueous-alcoholic sulphuric acid. 3-*Phenoxyisobutane*-1 : 2-*diol* had m. p. 91° (Found: C, 66·1; H, 7·6. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%); yield 42%.

(1*b*) 2-Methylallyl phenyl ether (74 g.) was added at 40° to a cooled solution of peracetic acid, prepared by heating hydrogen peroxide (114 g.) with acetic acid (280 c.c.) at 80° for 2 hours. The mixture was heated at 60°, and then became homogeneous. An exothermic reaction ensued, the temperature rising to 80° during 5 minutes. At this point the solution was cooled rapidly and poured into a large volume of water. The oil which separated was taken into chloroform and washed successively with water, dilute sodium carbonate solution, and again with water. Distillation then gave the following fractions; (*a*) b. p. 54—58°/1 mm. (23 g.); (*b*) b. p. 80—85°/1 mm. (25 g.). There was a residue (7 g.). Fraction (*a*) consisted of unchanged 2-methylallyl phenyl ether. Fraction (*b*) was mainly 1 : 2-epoxy-3-phenoxy*iso*butane. The yield of this was determined by adding the whole of the fraction (25 g.) to an excess of piperidine. The mixture was warmed to initiate the reaction, which soon occurred with evolution of heat, necessitating cooling. On distillation the product yielded piperidine, 2-methylallyl phenyl ether, and then 1-phenoxy-3-piperidino*iso*butan-2-ol, b. p. 134°/0·5 mm., identified by conversion into the *hydrochloride*, m. p. 150° (see below). The yield was 28 g., equivalent to a yield of 18·5 g. of 1 : 2-epoxy-3-phenoxy*iso*butane in fraction (*b*).

In a second similar experiment the mixture of 2-methylallyl phenyl ether and peracetic acid was allowed to react until the temperature reached 86°. This temperature was maintained for 2 minutes and then the product was isolated and distilled. The following fractions were obtained; (*a*) b. p. 52—60°/1 mm. (16 g.), (*b*) b. p. 60—85°/1 mm. (20 g.), (*c*) b. p. 85—130°/1 mm. (5 g.), (*d*) b. p. 140°/1 mm. (22 g.). Fraction (*a*) was mainly unchanged 2-methylallyl phenyl ether. Fraction (*b*) boiled mainly at 82°/1 mm. It contained 10·8 g. of 1 : 2-epoxy-3-phenoxy*iso*butane, because when it reacted with an excess of piperdine it gave 16·2 g. of 1-phenoxy-3-piperidino*iso*butan-2-ol, b. p. 135°/0·5 mm. Fraction (*c*) was warmed with a small volume of carbon tetrachloride. On cooling, crystals of 3-phenoxy*iso*butane-1 : 2-diol (11 g.) separated, m. p. 89—90° not depressed when mixed with an authentic sample. The mother-liquor was evaporated and the residue heated under reflux with aqueous-alcoholic sodium carbonate solution during 2 hours; ethyl acetate was formed. Water was added to the solution, and the product extracted by means of chloroform. The extract after being washed with water, concentrated, and mixed with light petroleum gave 3-phenoxy*iso*butane-1 : 2-diol (3·5 g.), m. p. 90° not depressed when mixed with an authentic sample.

(2) A mixture of phenol (20 g.) and β-methylglycidol (18·6 g.), heated at 90° for 2—3 hours with the addition of 2 or 3 drops of pyridine, gave white needles, m. p. 89—91° (24 g.), identical with the product obtained by oxidising 2-methylallyl phenyl ether. When pyridine ethiodide was substituted for pyridine and the condensation was conducted at 115° for 3 hours the yield was slightly improved (70%). Heating with pyridine ethiodide at 90—95° for 6·5 hours gave only a 12·5% yield of the product.

1-*Phenoxy*-3-*piperidinoisobutane*-2-*ol Hydrochloride*.—The product, b. p. 134°/0·5 mm., obtained by reaction of 1 : 2-epoxy-3-phenoxy*iso*butane with piperidine, was dissolved in aqueous hydrochloric acid, and the *hydrochloride* recovered by evaporation of the solution. It crystallised from ether–methanol in small, white plates, m. p. 150° (Found: N, 4·6; Cl, 12·2. $C_{15}H_{24}O_2NCl$ requires N, 4·9; Cl, 12·4%).

3-p-*Methoxyphenoxy*iso*butane*-1 : 2-*diol*.—*p*-Methoxyphenol (12·4 g.) and β-methylglycidol (8·8 g.), heated at 90—95° for 2 hours with the addition of pyridine (0·1 c.c.), afforded the *diol* (14·3 g.), m. p. 103—104°. A similar yield was obtained when the same reactants were heated at 115° for 3 hours or at 90—95° for 3 hours. The product was identical with that prepared from *p*-methoxyphenol and 3-chloro*iso*butane-1 : 2-diol; that had m. p. 104° (Found: C, 62·2; H, 7·5. $C_{11}H_{16}O_4$ requires C, 62·3; H, 7·6%).

3-(4-*Chloro*-3-*methylphenoxy*)iso*butane*-1 : 2-*diol*.—(1) 4-Chloro-3-methylphenyl 2-methylallyl ether (50 g.; see below) was added at 45° to a solution of peracetic acid prepared from acetic acid (240 c.c.) and hydrogen peroxide (100 vol; 75 g.). On being heated to 70° all the ether dissolved, and the reactants were kept at this temperature for an hour. The product was dissolved in ether–light petroleum, and the solution cooled in ice. A solid (A), m. p. 77—78° (7·85 g.), separated. The mother-liquor was evaporated and the residual oil hydrolysed, to give 19·2 g. of material (B), m. p. 78° (Found: C, 57·4; H, 6·7. $C_{11}H_{15}O_3Cl$ requires C, 57·3; H, 6·6%). Both the products (A) and (B) consisted of the almost pure 4-*chloro*-3-*methylphenyl ether* of methylglycerol.

The 4-*chloro*-3-*methylphenyl* 2-*methylallyl ether* used in this preparation as obtained in 75% yield by heating an equimolecular mixture of 4-chloro-3-methylphenol and 2-methylallyl chloride in aqueous alcohol in the presence of potassium hydroxide. It was an oil, b. p. 108°/1 mm. (Found: C, 67·0; H, 6·7. $C_{11}H_{13}OCl$ requires C, 67·15; H, 6·7%).

(2) The same diol was obtained in 65% yield when a mixture of β-methylglycidol (1 mol.) and 3-chloro-4-methylphenol (1·05 mol.) was heated for 3·5 hours at 90—95° in the presence of pyridine (0·01 mol. per 100 g. of reactants).

3-m-*Nitrophenoxy*iso*butane*-1 : 2-*diol*.—(1) 2-Methylallyl *m*-nitrophenyl ether (1 mol.) was oxidised during 4 hours at 70° with a solution of peracetic acid prepared from hydrogen peroxide (2·1 mols.). The product was isolated and then hydrolysed with aqueous-alcoholic sulphuric acid to 3-m-*nitrophenoxy*iso*butane*-1 : 2-*diol*, m. p. 68° (Found: C, 53·6; H, 6·3; N, 5·9. $C_{10}H_{13}O_5N$ requires C, 52·9; H, 5·7; N, 6·2%), in 33% yield. The 2-*methylallyl* m-*nitrophenyl ether* employed in this preparation was prepared in 45% yield by condensing equimolecular amounts of 2-methylallyl iodide and *m*-nitrophenol in aqueous alcohol in the presence of potassium hydroxide. The product was an oil, b. p. 95—98°/0·1 mm. (Found: C, 61·8; H, 5·9; N, 7·1. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·3%.

(2) The same diol was obtained in 10% yield by condensing *m*-nitrophenol (1·05 mols.) with β-methylglycidol (1·0 mol.) for 3·5 hours at 95° in the presence of pyridine (0·01 mol. per 100 g. of reactants).

3-m-*Carbobutoxyphenoxy*iso*butane*-1 : 2-*diol*.—2-Methylallyl chloride (20 g.) was added to a solution containing butyl *m*-hydroxybenzoate (38·8 g.) and potassium hydroxide (11·2 g.) in a mixture of alcohol (200 c.c.) and water (25 c.c.), and the whole heated under reflux for 75 minutes; the resulting m-*carbobutoxyphenyl* 2-*methylallyl ether* (31·1 g.; 62%) was isolated as a colourless, viscous oil, b. p. 153—154°/1 mm. (Found: C, 72·2; H, 7·9. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%).

The product (30 g.) was added at 35° to a solution of peracetic acid prepared from acetic acid (80 c.c.) and hydrogen peroxide (100-vol.; 25 g.). When warmed to 70° the mixture became homogeneous. It was kept for an hour at 70—75° and then the product was treated as described for the 3-*m*-tolyloxy-analogue (1*a*, p. 2879). The *diol* was obtained as a pale yellow, viscous oil, and this was heated at 90° for 2 hours at 1 mm., but not distilled (Found: C, 63·1; H, 7·7. $C_{15}H_{22}O_4$ requires C, 63·8; H, 7·9%).

3-p-*Carbobutoxyphenoxy*iso*butane*-1 : 2-*diol* was prepared similarly by oxidising butyl *p*-2-methylallyloxybenzoate (1 mol.) during 3—4 hours at 70° with peracetic acid prepared from acetic acid and hydrogen peroxide (100-vol.; 2·1 mols.), the product being finally hydrolysed with aqueous-alcoholic sulphuric acid. The diol (yield, 50%) has m. p. 56° (Found: C, 63·5; H, 7·7%). The *butyl* p-2-*methylallyloxybenzoate* used in this preparation was obtained in 40% yield by condensing equimolecular amounts of butyl *p*-hydroxybenzoate and 2-methylallyl chloride in acetone in the presence of anhydrous potassium carbonate. It was an oil, b. p. 218—220°/33 mm. (Found: C, 72·1; H, 7·8. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%).

None of the β-methylglycerol derivative could be isolated from a similar oxidation of p-2-*methylallyloxybenzoic acid*, which was prepared (yield 90%) by condensing equimolecular amounts of *p*-hydroxybenzoic acid and 2-methylallyl chloride in alcoholic potassium hydroxide. It had m. p. 132° (Found: C, 67·9; H, 6·4. $C_{11}H_{12}O_3$ requires C, 68·5; H, 6·3%).

3-p-*Tolyloxy*iso*butane*-1 : 2-*diol*.—(1) 2-Methylallyl *p*-tolyl ether (1 mol.) was heated at 65—70° during 2·5 hours with peracetic acid prepared from hydrogen peroxide (2·1 mols.). The reaction product was isolated and heated with aqueous-alcoholic sulphuric acid, then recovered and crystallised from carbon tetrachloride. The *diol* was obtained as needles, m. p. 106° (Found: C, 67·7; H, 8·2. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%).

(2) A solution of peracetic acid was prepared from hydrogen peroxide (100-vol.; 171 g.) and acetic acid (420 c.c.), and then 2-methylallyl *p*-tolyl ether (121·5 g.) was added at 50°. The temperature rose to 80° during 12 minutes and at this point the solution was cooled, kept at 35° for an hour, and then added to water (2 vols.). The precipitated oil was extracted by chloroform (4 × 250 c.c.), isolated, and distilled. The following fractions were obtained: (*a*) b. p. 58°/0·7 mm. (36 g.); (*b*) b. p. 58—72°/0·5 mm. (12 g.); (*c*) b. p. 80°/0·5 mm. (17 g.); (*d*) b. p. 140—155°/1—2 mm. (37 g.). Fraction (*a*) was mainly 2-methylallyl *p*-tolyl ether, fraction (*c*) mainly 1 : 2-epoxy-3-*p*-tolyloxyiso*butane*, and fraction (*b*) contained both these constituents. Fraction (*d*) was a viscous oil. Fraction (*c*) was characterised by reaction with diethylamine in slight excess. 1-*Diethylamino*-3-*p*-*tolyloxy*iso*butan*-2-*ol*

was formed readily. It was obtained by distillation as a pale yellow oil, b. p. 146°/0·5 mm. (Found: C, 72·1; H, 9·9; N, 5·6. $C_{14}H_{21}O_3N$ requires C, 71·7; H, 10·0; N, 5·6%). Fraction (*d*) crystallised from carbon tetrachloride, yielding 3-*p*-tolyloxy*iso*butane-1 : 2-diol (14 g.), m. p. 104—105°, unchanged when mixed with an authentic sample. The mother-liquor was evaporated, and the residue heated with dilute alcoholic sulphuric acid. The hydrolysed residue was recovered and recrystallised from carbon tetrachloride. In this way an additional 10·5 g. of the ether, m. p. 104—105°, were obtained.

Hydrolysis of 1 : 2-*epoxy*-3-*p*-*tolyloxyisobutane*. Fraction (*c*) was redistilled to give the pure glycide ether, which (4·45 g.) was heated with a mixture of glacial acetic acid (14 c.c.) and water (5·7 c.c.) for 2 hours at 95°. The product was isolated by pouring the mixture into water, extraction into chloroform, and recovery. It was then crystallised from carbon tetrachloride, yielding 1·8 g. of the ether, m. p. 104—105°. The mother-liquor was evaporated, and the residue heated with alcoholic sulphuric acid. After addition of water, extraction into chloroform, recovery, and crystallisation from carbon tetrachloride, an additional 1·5 g. of the ether, m. p. 104—105°, were obtained.

In a similar experiment the same amount of the glycide ether was caused to react under the same conditions with peracetic acid prepared from acetic acid (14 c.c.) and hydrogen peroxide (100-vol; 5·7 c.c.). Crystallisation of the product from carbon tetrachloride afforded the ether (1·6 g.), m. p. 105—106°, and more (1·3 g.) of the same ether resulted when the mother-liquor was evaporated and the residue hydrolysed by means of alcoholic sulphuric acid.

(3) A mixture of *p*-cresol (21·6 g.) and β-methylglycidol (17·6 g.) containing two drops of pyridine was heated at 90—95° for 3·5 hours. 3-*p*-Tolyloxy*iso*butane-1 : 2-diol (28 g.), m. p. 105°, was obtained after crystallisation of the product from carbon tetrachloride. An almost identical yield was obtained when the pyridine was replaced by its ethiodide, and the reaction carried out at 115° for 3 hours.

3-p-*Chlorophenoxyisobutane*-1 : 2-*diol*.—(1) *p*-Chlorophenyl 2-methylallyl ether (1 mol.) was heated at 70° for 3—4 hours with a solution of peracetic acid, prepared from 2·1 mols. of hydrogen peroxide. The product was isolated, and then heated with a 1% solution of concentrated sulphuric acid in 50% aqueous alcohol. The *diol* thus obtained crystallised from carbon tetrachloride, m. p. 103° (Found: C, 55·7; H, 6·1. $C_{10}H_{13}O_3Cl$ requires C, 55·4; H, 6·1%).

(2) *p*-Chlorophenyl 2-methylallyl ether (91·3 g.) was added to a solution of peracetic acid prepared from glacial acetic acid (280 c.c.) and hydrogen peroxide (100-vol.; 114 g.). The mixture was heated at 67° until it became homogeneous (2 minutes), and then the temperature was allowed to rise during 4 minutes to 85°. The product was quickly cooled to 30°, kept at this temperature for 3 hours, and then poured into water. The precipitated oil was taken up in chloroform, washed, dried, and distilled. The following fractions were obtained: (*a*) b. p. 80—100°/1 mm. (20 g.); (*b*) b. p. 100—120°/1 mm. (30·5 g.); (*c*) b. p. 120—170°/1 mm. Fraction (*a*) was mainly *p*-chlorophenyl 2-methylallyl ether. Fraction (*b*) distilled mainly at 112°/1 mm. and again at this temperature on redistillation. It was 3-*p*-chlorophenoxy-1 : 2-epoxy*iso*butane, as shown by its conversion into 1-diethylamino-3-*p*-chlorophenoxy*iso*butan-2-ol by reaction with diethylamine. Fraction (*c*) crystallised from carbon tetrachloride yielding 3-*p*-chlorophenoxy*iso*butane-1 : 2-diol (18 g.), m. p. 101—102° not depressed on admixture with the product of preparation (1). The mother-liquor gave a tacky residue on evaporation, and this was heated under reflux with a 1% solution of concentrated sulphuric acid in 50% aqueous alcohol. After isolation of the hydrolysed product and recrystallisation from carbon tetrachloride an additional 9·1 g. of 3-*p*-chlorophenoxy*iso*butane-1 : 2-diol, m. p. 100—101°, were obtained.

(3) A solution of potassium permanganate (15·8 g.) in water (1 l.) was added during 1 hour to a stirred solution of *p*-chlorophenyl 2-methylallyl ether (27·4 g.) in acetone (300 c.c.), the temperature being kept at 0°. The oxidation complete, the precipitated manganese dioxide was filtered off and washed with chloroform. The filtrate was extracted by means of chloroform, and the combined chloroform solutions were evaporated. The residue (2 g.) crystallised from carbon tetrachloride in small feathery plates, m. p. 102—103° not depressed on mixing with 3-*p*-chlorophenoxy*iso*butane-1 : 2-diol obtained as in (2), above.

(4) *p*-Chlorophenol (1·05 mols.) and β-methylglycidol (1·0 mol.) were heated at 90—95° for 3·5 hours in the presence of pyridine (0·01 mol. per 100 g. of total reactants). The product, crystallised from carbon tetrachloride, was obtained, m. p. 98—100°, in 60% yield. When an equimolecular amount of pyridinium ethiodide was used at 115° in this preparation instead of pyridine an almost identical yield was obtained.

Action of Acetic Acid on 3-p-*Chlorophenoxyisobutane*-1 : 2-*diol*.—A solution containing this diol (10·8 g.) in a mixture of acetic acid (28 c.c.) and water (11·4 c.c.) was heated at 95° for 5 hours, then cooled and added to water, and the product extracted by means of chloroform. The chloroform was evaporated, and the residue crystallised from carbon tetrachloride. 3-*p*-Chlorophenoxy*iso*butane-1 : 2-diol (8·2 g.), m. p. 103°, was recovered by this means. The mother-liquor was concentrated and then mixed with light petroleum. Crystals, m. p. 60—62°, slowly separated (1·5 g.). The product recrystallised from light petroleum (b. p. 40—80°) in small, hard, white prisms, m. p. 65—66° (Found: C, 55·6; H, 5·8; Cl, 13·4. $C_{12}H_{15}O_4Cl$ requires C, 55·7; H, 5·9; Cl, 13·7%). This compound was 3-p-*chlorophenoxyisobutane*-1 : 2-*diol monoacetate*.

In several similar experiments the concentration of the acetic acid employed was varied. In each experiment heating was carried out under reflux for 8 hours. The proportions of methylglycerol ether recovered and *O*-acetate formed were:

Concn. of acetic acid (% by vol.)	100	72·1	51·2
Methylglycerol ether recovered, %	None	50	77·8
Methylglycerol ether *O*-acetate isolated, %	85	36·4	11·6

Action of Acetic and Peracetic Acids on 3-p-*Chlorophenoxy*-1 : 2-*epoxyisobutane*.—(1) The epoxide (9·98 g.) was added to 2 mols. of peracetic acid prepared from acetic acid (28 c.c.) and hydrogen peroxide (100-vol.; 11·4 g.). The mixture was heated for an hour at 75°, then diluted, and the product extracted by means of chloroform. The chloroform solution was washed and then concentrated, and light petroleum was added to turbidity. Crystals of 3-*p*-chlorophenoxy*iso*butane-1 : 2-diol, m. p. 100—101°, separated (4·3 g.). The mother-liquor was evaporated and the residue heated for an hour with a 1% solution of concentrated sulphuric acid in 50% aqueous alcohol. The hydrolysed product was extracted by means of chloroform; it crystallised when light petroleum was added. A second crop (2·3 g.) of the diol, m. p. 100—101°, was thus obtained. The second crop being assumed to have been derived by hydrolysis of an acetate, the yields of the methylglycerol ether obtained at the two stages indicate that the methylglycerol ether and its *O*-acetate were formed in the ratio 1·87 : 1 by the action of a solution of peracetic acid in acetic acid on 3-(*p*-chlorophenoxy)-1 : 2-epoxy*iso*butane.

(2) In a similar experiment in which the solution of peracetic acid was replaced by a mixture of acetic acid (28 c.c.) and water (11·4 c.c.) the yield of 3-*p*-chlorophenoxy*iso*butane-1 : 2-diol first obtained was 5·0 g. Hydrolysis of the non-crystallising constituent then afforded an additional 2·4 g. of the same methylglycerol ether. The relative amounts of 3-*p*-chlorophenoxy*iso*butane-1 : 2-diol obtained at the two stages indicate the formation of the methylglycerol ether and its *O*-acetate in the ratio 2·04 : 1 by the action of acetic acid on 3-*p*-chlorophenoxy-1 : 2-epoxy*iso*butane.

3-p-*Chlorophenoxy*-1-*diethylamino*iso*butan*-2-*ol*.—Fraction (*b*), b. p. 112°/1 mm., obtained in the oxidation of *p*-chlorophenyl 2-methylallyl ether by means of peracetic acid (p. 2882) reacted with diethylamine with evolution of heat. The *adduct* was obtained as a yellow oil, b. p. 155°/0·5 mm. (Found: C, 62·15; H, 8·1; N, 4·7; Cl, 13·2. $C_{14}H_{22}O_2NCl$ requires C, 61·8; H, 8·2; N, 5·2; Cl, 13·1%).

3-*Chloro*iso*butane*-1 : 2-*diol*.—(1) To a solution of peracetic acid prepared from acetic acid (1500 c.c.) and hydrogen peroxide (100-vol.; 450 g.) was added 2-methylallyl chloride (181 g.). The mixture was kept at 25° for 5 days and then concentrated under reduced pressure. Distillation gave: (*a*) unchanged 2-methylallyl chloride (10 g.); (*b*) a fraction, b. p. 70—80°/1 mm. (10—12 g.); (*c*) 3-chloro*iso*butane-1 : 2-diol and its *O*-acetate, b. p. 79—80°/0·5 mm. (170—175 g.); (*d*) a fraction of higher b. p. (25—30 g.).

(2) The same reactants, mixed at the room temperature and then heated at 70° for an hour, gave the following products: (*a*) unchanged 2-methylallyl chloride (30 g.); (*b*) 3-chloro*iso*butane-1 : 2-diol and its *O*-acetate, b. p. 78—83°/0·5 mm. (140—145 g.); (*c*) a higher-boiling fraction (20 g.).

The mixture of 3-chloro*iso*butane-1 : 2-diol and its *O*-acetate (60 g.), obtained under either of the conditions described, was heated under reflux for an hour with a 1% solution of concentrated sulphuric acid in 50% aqueous alcohol. The yield of recovered 3-chloro*iso*butane-1 : 2-diol was 48 g.

β-*Methylglycidol*.—A solution of potassium hydroxide (56 g.) in dry ethanol (200 c.c.) was added dropwise to a solution of 3-chloro*iso*butane-1 : 2-diol (125 g.) in alcohol (100 c.c.), which was cooled in water to keep the temperature at 13—15°. The mixture was kept for 20 minutes after the addition was complete. It was then filtered, and the filtrate concentrated to half volume under reduced pressure. Salts were then precipitated by adding ether (2 vols.) to the residue. The suspension was filtered, and the filtrate distilled. The fraction, b. p. 70—85°/18—20 mm., was collected and redistilled to give pure β-methylglycidol, b. p. 80°/21 mm. (70 g., 80%).

Several condensations of phenols with 3-chloro*iso*butan-1 : 2-diol, not describe above, are summarised in the attached table.

Reactants						Products						
							Found, %:			Reqd., %:		Yield
Phenol deriv.	Wt. (g.)	Diol (g.)	EtOH (c.c.)	K_2CO_3 (g.)	Reflux time (hr.)	M. p.	C	H	Formula	C	H	(g.)
m-Me	5·4	7·8	50	6·9	3	—	—	—	—	—	—	6·1
3 : 5-Me_2	24·4	24·9	250	27·6	4	77	—	—	—	—	—	21·7
o-Cl	21·5	31·2	150	34·5	3	56 *	55·0	6·1	$C_{10}H_{13}O_3Cl$	55·4	6·1	—
o-I	22	15·6	150	35	3	71 *	39·1	4·0	$C_{10}H_{13}O_3I$	39·0	4·3	22
p-I	22	15·6	150	35	3	106 †	39·2	4·2	"	"	"	24·6
o-OMe	30	40	150	40	4	77 *	62·4	7·7	$C_{11}H_{16}O_4$	62·3	7·6	—
m-OMe	30	33	150	35	3	90 †	62·3	7·4	"	"	"	—
p-OMe	22	30	150	30	3	104 †	62·2	7·5	"	"	"	15
p-NHAc	21·5	19·8	150	27·6	5	147 *	60·2	7·0 ‡	$C_{12}H_{17}O_4N$	60·2	7·2	26

* Needles. † Prisms. ‡ Found: N, 5·5. Reqd.: N, 5·9%.

The authors thank the Directors for permission to publish the results of this work, which was carried out during the period 1944—1948.

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London, N.1. [*Received, February 12th*, 1951.]

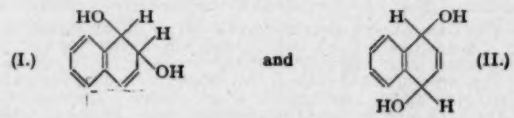
642. *Ultra-violet Absorption Spectra of Some Metabolites of Naphthalene, Anthracene, and Phenanthrene.*

By R. N. Beale and E. M. F. Roe.

The ultra-violet absorption spectra of metabolites of naphthalene, anthracene, and phenanthrene in rabbit and rat have been measured. Comparison with relevant reference compounds confirms the structure of the naphthalene metabolite to be 1 : 2-dihydro-1 : 2-dihydroxynaphthalene, that of the anthracene metabolite from rat and rabbit to be 1 : 2-dihydro-1 : 2-dihydroxyanthracene, and those of the phenanthrene metabolites from the rabbit to be 9 : 10-dihydro-9 : 10- and 1 : 2-dihydro-1 : 2-dihydroxyphenanthrene and from the rat 9 : 10-dihydro-9 : 10-dihydroxyphenanthrene.

In order to assist in the elucidation of the chemical structures of dihydrodihydroxy-derivatives produced during the metabolism of the hydrocarbons naphthalene, anthracene, and phenanthrene by rabbits and rats (Boyland and Levi, *Biochem. J.*, 1935, **29**, 2679; Booth and Boyland, *ibid.*, 1949, **44**, 361; Boyland and Wolf, *ibid.*, 1950, **47**, 64) the spectra of these substances have been measured and compared with those of relevant reference compounds. The compounds were examined in alcoholic solutions, both spectrographic and spectrophotometric techniques being used.

Naphthalene Metabolites.—Optically active and inactive *trans*-stereo-isomers were isolated as metabolic products of naphthalene from the rat and the rabbit, and these compounds give spectra of the same general shape (Fig. 1 and Table I). There are clearly two most probable structures for these metabolites, *i.e.*, (I) and (II). These should be easily distinguishable spectroscopically, for (I) should have a spectrum resembling that of 1 : 2-dihydronaphthalene,



i.e., of the styrene type, while the spectrum of (II) would resemble that of 1 : 4-dihydronaphthalene or of tetralin, *i.e.*, of the *o*-xylene type. The data for these compounds are compared in Table I and indicate structure (I) as the correct formula for the metabolite, in accordance with the chemical evidence (Booth and Boyland, *loc. cit.*). Further, a synthetic specimen of the racemic 1 : 2-dihydro-1 : 2-dihydroxynaphthalene (Booth, Boyland, and Turner, *J.*, 1950, 1188) has a spectrum (Fig. 1; Table I) of the same type as that of the racemic

Table I.

Compound	$\lambda_{max.}$, mμ.	$\varepsilon_{max.}$ (mol.)
Styrene	244	11,000 [1]
1-Propenylbenzene	248	14,900 [2]
Indene	246	10,000 [3]
1 : 2-Dihydronaphthalene	262	10,230 [3]
o-Xylene	263	270 [4]
Tetralin	~267	740 [3]
1 : 4-Dihydronaphthalene	~267	800 [3]
1 : 2-Dihydro-1 : 2-dihydroxynaphthalene (synthetic racemate, m. p. 103°)	263	6,830
" " " (rabbit, racemate, m. p. 100°) ...	263	7,850
" " " (rabbit, optically active, m. p. 126°)	265	8,410
" " " (rat, racemate, m. p. 101°)	264·5	7,790
" " " (rat, optically active, m. p. 126°)	265	8,100

[1] Arends, *Ber.*, 1931, **64**, 1936. [2] Koch, *J.*, 1948, 1123. [3] Morton and de Gouveia, *J.*, 1934, 911. [4] Wolf and Herold, *Z. physikal. Chem.*, 1931, *B*, **13**, 201.

rabbit metabolite; the discrepancy in extinction values must be due to impurity in one or both of the compounds. The spectrum confirms structure (I) as the formula for the metabolic 1 : 2-dihydro-1 : 2-dihydroxynaphthalenes.

It is of interest to note the spectral changes in these compounds caused by cyclisation involving the double bond conjugated to the benzene chromophore. Thus, from Table I it is seen that styrene and 1-propenylbenzene have similar spectral characteristics, while in 1 : 2-dihydronaphthalene a considerable bathochromic shift occurs with little change in maximum extinction. This wave-length shift is not found in the spectrum of indene, where cyclisation involves a five-membered ring.

In the early work on the chemistry and spatial configuration of the naphthalene metabolites (Booth and Boyland, *loc. cit.*) these compounds were hydrogenated to the corresponding 1 : 2 : 3 : 4-tetrahydro-1 : 2-dihydroxy-derivatives, and the spectrum of one of them (hydrogenated racemate, m. p. 111°, from rabbit; Fig. 2) was examined, together with those

FIG. 1.

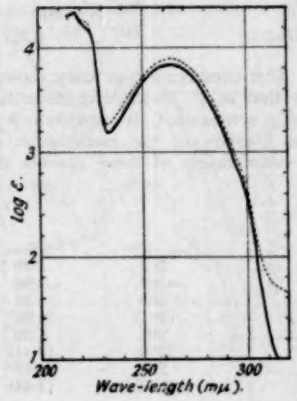


FIG. 2.

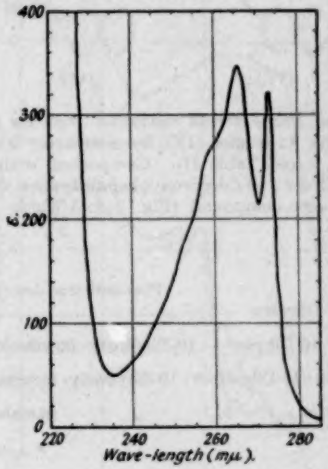


FIG. 1.

1 : 2-*Dihydro*-1 : 2-*dihydroxynaphthalenes* : ——— *synthetic* trans-(*racemate*); – – – *metabolite* (*racemate*) *from rabbit.*

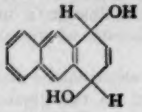
FIG. 2.

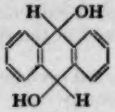
Hydrogenated naphthalene metabolite (racemate) from rabbit.

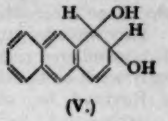
of the hydrogenated synthetic *cis*- and *trans*-racemates. The reduction in extinction which occurs when the ($\Delta^{3:4}$)-conjugated double bond is saturated is as expected, the resulting spectrum resembling that of an alkylbenzene, cf. *o*-xylene (Table I). The spectra are almost the same for the three racemates although there is somewhat closer agreement between those of the synthetic *trans*-isomer and the hydrogenated metabolite than between the latter and the synthetic *cis*-compound. The differences in $\varepsilon_{max.}$ (of the order of 3%) are probably not significant, but the closer agreement between the values of $\lambda_{max.}$ for the synthetic *trans*-compound and the hydrogenated metabolite may be significant (hydrogenated metabolite 272·8 and 265·4 mμ.; *trans*-compound, 272·8 and 265·5 mμ.; *cis*-compound, 272·3 and 265·3 mμ.). Unequivocal spectroscopic differentiation between the *cis*- and the *trans*-derivatives is not possible.

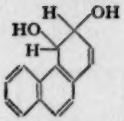
Anthracene and Phenanthrene Metabolites.—One anthracene and two phenanthrene diols were isolated by metabolism of the corresponding hydrocarbons. In the case of the anthracene diol three structures may be postulated, namely, (III)—(V). Chemical evidence (Boyland and Levi, *loc. cit.*) and spectroscopic evidence also (see below) show that (III) and (IV) are impossible structures for this diol. For the phenanthrene diols there are four possible structures, namely, (VI)—(IX). Of these, chemical evidence (Boyland and Wolf, *loc. cit.*) shows that (VI) and (VII) are impossible and that (IX) is the sole product from the rat and

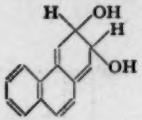
(VIII) and (IX) both result from metabolism in the rabbit. Spectroscopic evidence (see below) supports these conclusions.

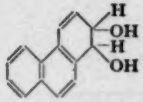

(III.)

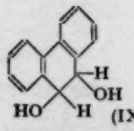

(IV.)


(V.)


(VI.)


(VII.)


(VIII.)


(IX.)

(a) *Phenanthrene metabolite from the rat and rabbit.* This compound was early shown to be the 9 : 10-diol (IX) by comparing its spectrum with that of 9 : 10-dihydrophenanthrene (Fig. 3 and Table II). Comparison with the more recently synthesised *cis*- and *trans*-9 : 10-dihydro-9 : 10-dihydroxyphenanthrenes demonstrated the identity of the metabolites with the *trans*-compound (Fig. 3 and Table II). From an examination of these spectra there

TABLE II.

Phenanthrene deriv.	$\lambda_{max.}$, mμ.	log $\varepsilon_{max.}$
9 : 10-Dihydro-	262	4·20 *
	~289	~3·60
cis-9 : 10-Dihydro-9 : 10-dihydroxy- (synthetic)	269	4·21
	(281)	(4·04)
trans-9 : 10-Dihydro-9 : 10-dihydroxy- (synthetic)	268	4·20
	(300)	(3·41)
„ „ „ (metabolite, rat)	267	4·19
	(300)	(3·44)

* Askew, *J.*, 1935, 512.

appears to be interaction of the hydroxyl groups with the aromatic rings in spite of the intervening saturated carbon atoms, since introduction of these groups in 9 : 10-dihydrophenanthrene causes a bathochromic shift in the spectrum of 50—70 A. (Fig. 3). Further, in the case of the synthetic *cis*- and *trans*-diols, there are small but distinct differences between the spectra; *i.e.*, the pronounced shoulder at 300 mμ. in the *trans*-spectrum is missing in the *cis*-spectrum, where a new shoulder is apparent at 281 mμ.; and the minimum at 240 mμ. in the *cis*-spectrum is considerably reduced in extinction compared with that of the *trans*-diol. Consideration of atom models of the isomers shows that in the *cis*-diol there is steric interference between one or other hydroxyl group and its neighbouring hydrogen atom on the aromatic ring, and that this hindrance is dependent on the configuration of the asymmetric carbon atoms. In the *trans*-diol there is either free rotation or steric hindrance for *both* hydroxyl groups, so that the differences in fine structure of the two spectra may probably be attributed to the differing degree of steric hindrance to the interaction of the hydroxyl groups in these two isomers.

(b) *Further phenanthrene metabolite from rabbit and anthracene metabolite from rat and rabbit.* Since chemical evidence indicated (VIII) as the structure for this second phenanthrene metabolite and (V) as that for the anthracene metabolite from rat and from rabbit, search was made for the spectra of relevant reference compounds. No corresponding hydroaromatic derivatives were available, so it was necessary to consider the data for naphthalene derivatives with conjugated substituents at the 1- and 2-positions. Thus the spectrum of (VIII) should resemble that of 1-propenylnaphthalene and that of (V) the spectrum of 2-propenylnaphthalene, for example. The only spectra of this type already recorded were those of 2-vinylnaphthalene (Laitinen, Miller, and Parkes, *J. Amer. Chem. Soc.*, 1947, **69**, 2707; see Table III) and of 1-propenylnaphthalene (Pestemer and Manchen, *Monatsh.*, 1936, **68**, 92).

The two isomeric propenylnaphthalenes were therefore synthesised, by the courtesy of Professor G. A. R. Kon and G. W. Spickett (*J.*, 1949, 2725), and the spectral data are recorded in Fig. 4 and Table III. There was good agreement with Pestemer and Manchen's data for the 1-propenyl) derivative. The spectral details of further naphthalene derivatives listed in Table III illustrate the different effects of substitution at the 1- and 2-positions in the molecule. The differences are small for methyl and chloro-substituents but much greater for strongly interacting conjugating groups. Data for derivatives with strongly polar substituents are omitted since these have different effects. They will be discussed in a later communication.

FIG. 3.

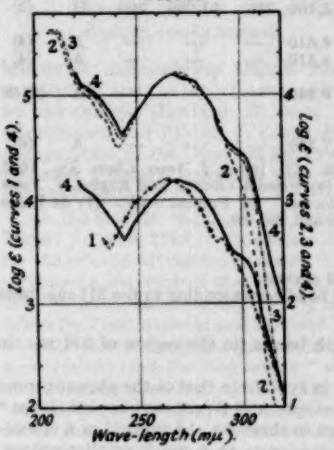


FIG. 4.

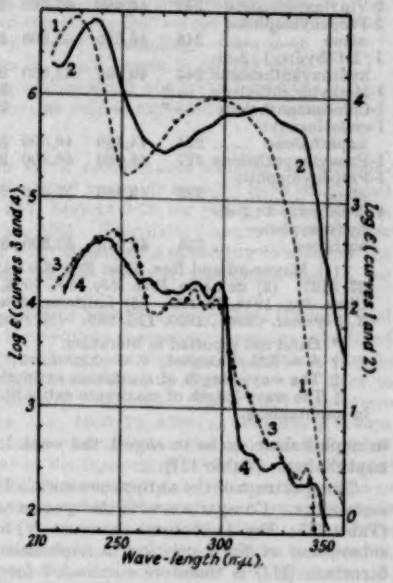


FIG. 3.

9 : 10-*Dihydrophenanthrene* – – O – – O – – (1).
9 : 10-*Dihydro*-9 : 10-*dihydroxyphenanthrene* : *synthetic* (cis) – – – – – – – – (2).
" " " *synthetic* (trans) — · — · — · — (3).
" " " *metabolite* (trans) *from rat* ———— (4).

FIG. 4.

1-*Propenylnaphthalene* – – – – – – – (1).
Phenanthrene metabolite from rabbit – ———— (2).
2-*Propenylnaphthalene* – – O – – O – – (3).
Anthracene metabolite from rabbit ——O——O—— (4).

Comparison of the spectrum of the phenanthrene metabolite with those of 1-substituted naphthalenes (Table III and Fig. 4) confirms structure (VIII) for this compound. The spectrum is similar to that of 1-propenylnaphthalene but is shifted considerably to longer wave-lengths, owing in part to cyclisation involving the unsaturated side-chain and to the presence of the two hydroxy-groups (see p. 2885). Slight steric hindrance in the 1-propenylnaphthalene (expected from chemical evidence to be the *trans*-methyl compound) probably enhances this wave-length difference. The spectra of the more strongly hindered 1-phenyl- and 1-*cyclo*hexenyl-naphthalenes suffer an even larger hypsochromic shift compared with the 1-propenyl derivative, and with the phenanthrene metabolite in which the conjugated double bond is coplanar with the naphthalene residue. All of these derivatives show the changes typical of substitution of a strongly interacting group at the 1-position in naphthalene, *i.e.*, a large bathochromic shift and loss of fine structure of the middle band system at 275 mμ.

TABLE III.

Band System.

	A			B			C				
Compound	λ, mμ.	ν, cm.$^{-1}$	ε	λ, mμ.‡	ν, cm.$^{-1}$	ε	λ, mμ.§	ν, cm.$^{-1}$	ε	Solvent †	Ref.
Naphthalene	220·5	45,350	110,650	275	36,360	5,660	311	32,150	249	A	(1)
2-Methylnaphthalene	224	44,640	104,700	276	36,230	4,790	319	31,350	510	A	(2)
2-Chloronaphthalene	—*	—	—	277·5	36,050	4,000	321	31,130	400	H	(3)
2-Phenylnaphthalene	248	40,320	50,100	286	34,960	12,000	—*	—	—	A	(4)
2-Vinylnaphthalene	247	40,485	47,500	285	35,090	14,800	—*	—	—	C	(5)
2-Propenylnaphthalene	246	40,650	51,300	285	35,090	13,850	341	29,325	282	A	(6)
1 : 2-Dihydro-1 : 2-dihydroxyanthracene	244	40,985	42,650	286·5	34,905	16,600	344	29,070	195	A	(6)
1-Methylnaphthalene	—*	—	—	282·5	35,400	5,000	313·5	31,890	240	H	(7)
1-Chloronaphthalene	—*	—	—	284·5	35,160	5,150	320	31,260	200	H	(3)
1-*cyclo*Hexenylnaphthalene	225	44,450	40,000	281	35,590	6,610	—	—	—	A	(4)
1-Phenylnaphthalene	227	44,060	56,200	288	34,720	8,510	—	—	—	A	(4)
1-Propenylnaphthalene	228	43,860	53,600	296	33,785	9,340	—	—	—	A	(6) (8)
1 : 2-Dihydro-1 : 2-dihydroxyphenanthrene	238	42,015	52,300	316	31,650	7,730	—	—	—	A	(6)

(1) Mayneord and Roe, *Proc. Roy. Soc.*, 1935, *A*, **152**, 299. (2) Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127. (3) de Lazlo, *Proc. Roy. Soc.*, 1926, *A*, **111**, 355. (4) Friedel, Orchin, and Reggel, *J. Amer. Chem. Soc.*, 1948, **70**, 199. (5) Laitinen, Miller, and Parkes, *loc. cit.* (6) Present work. (7) de Lazlo, *Z. physikal. Chem.*, 1925, **118**, 369. (8) Pestemer and Manchen, *loc. cit.*

* Band not reported in literature.
† A = Ethyl alcohol; C = chloroform; H = hexane.
‡ The wave-length of maximum extinction of this band system.
§ The wave-length of maximum extinction of the strong band corresponding to the 311-mμ. band in naphthalene.

in naphthalene, so as to engulf the weak long-wave-length bands (in the region of 311 mμ. in naphthalene; Table III).

The spectrum of the anthracene metabolite is different in type from that of the phenanthrene metabolite. Comparison with the spectra of 2-phenyl-, 2-vinyl-, and 2-propenyl-naphthalenes * (Table III; Fig. 4) confirms structure (V) for this diol from anthracene. A methyl or a chloro-substituent at the 2-position in naphthalene affects the spectrum to a much smaller extent. Structure (III) is therefore eliminated for this metabolite since its spectrum would resemble that of 2-methylnaphthalene or, more closely, 2 : 3-dimethylnaphthalene. In all of these compounds, division of the spectrum into three distinct band systems remains, as in naphthalene, an effect typical of 2-substitution in this molecule. Structure (IV) is readily eliminated on spectroscopic grounds since its spectral characteristics should resemble those of *o*-xylene (Table I).

In spite of the origin of the last metabolite in anthracene, its spectrum is remarkably similar to that of phenanthrene (Mayneord and Roe, *loc. cit.*) and this is also true to a smaller extent of the 2-propenylnaphthalene. This probably indicates a marked change of symmetry in the naphthalene molecule on substitution, resulting in changes in the directions of polarisation of the electric vector of the absorbed light. The significance of this will be discussed later.

This investigation has been supported by grants to the Royal Cancer Hospital from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the Research Grants Division of the United States Public Health Service. Our thanks are offered to Professor E. Boyland and his colleagues for providing the majority of the compounds examined in this investigation, and to Mr. F. C. Middleton for assistance in some of the spectrophotometric measurements.

THE CHESTER BEATTY RESEARCH INSTITUTE,
ROYAL CANCER HOSPITAL, LONDON, S.W.3.

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* Atom models show the same small degree of steric hindrance in the 2-vinyl- and the *trans*-2-propenyl-naphthalenes and greater hindrance in the *cis*-2-propenylnaphthalene. The close similarity between the spectra of the first two compounds indicates the *trans*-structure for the 2-propenyl derivative.

643. *Magnetochemistry of the Heaviest Elements. Part V.* Uranium Tetrafluoride–Thorium Tetrafluoride Solid Solutions.*

By J. K. Dawson.

The magnetic susceptibilities of solid solutions of uranium tetrafluoride and thorium tetrafluoride have been measured over the temperature range 90—350° K., and at all dilutions the susceptibility of the U(IV) ion obeys the Weiss–Curie law. At infinite dilution the extrapolated susceptibility and the magnetic moment of U(IV) are close to the theoretical values predicted for a $5f^2$ electron configuration with the *j–j* type of coupling. This is in contrast to the corresponding oxide system in which urania is diluted with thoria, since the susceptibility and the magnetic moment of U(IV) at infinite dilution in that case correspond to theoretical values expected for a $6d^2$ electron configuration.

Magnetic susceptibility studies have been made on a considerable number of uranium compounds, and the reported magnetic moments of the U(IV) ion range from 2·7 Bohr magnetons for the chloride (Bommer, *Z. anorg. Chem.*, 1941, **247**, 249) to 3·75 for the hydrated oxalate (Hutchinson and Elliott, *J. Chem. Physics*, 1948, **16**, 920). Speculation about the electronic configuration of the U(IV) ion has favoured a $6d^2$ or a $5f^2$ stable state according to whether the observed magnetic moments have been respectively at the lower or the higher end of the observed range.

In the dioxide, the U(IV) ion has a magnetic moment of 3·20 Bohr magnetons (Dawson and Lister, *J.*, 1950, 2188). This value is intermediate between the theoretical moments calculated for the $5f^2$ and $6d^2$ electronic states, but dilution with isomorphous diamagnetic thorium dioxide produces a lowering of the moment, and the susceptibility at infinite dilution is very close to that obtained theoretically by the use of the " spin-only " formula. These facts have been taken by Trzebiatowski and Selwood (*J. Amer. Chem. Soc.*, 1950, **72**, 4504) as evidence in favour of a $6d^2$ electron configuration. The magnetic moment of uranium tetrafluoride is somewhat more remote from the " spin-only " value and nearer to the theoretical value expected for a $5f^2$ configuration (Dawson, *J.*, 1951, 429), and it was of interest to apply the dilution technique to this compound in order to determine whether the change of ionic environment from the oxide to the fluoride had any effect on the ground state of the uranous ion. The dilution was made with diamagnetic thorium tetrafluoride which is isomorphous with the uranium compound; they are both monoclinic and their cell dimensions differ by only about 3% (Zachariasen, U.S. Atomic Energy Commission Report, M.D.D.C. 1151).

Experimental.

The starting materials were commercial grades of uranyl sulphate and thorium nitrate. The uranyl sulphate was dissolved in a mixture of concentrated sulphuric acid and ethyl alcohol and reduced to the quadrivalent state by irradiation with ultra-violet light (for details, see Hutchinson and Elliott, *loc. cit.*). The insoluble uranous sulphate was centrifuged, washed with absolute ethyl alcohol, and dried in air at 80°. Analyses for uranium and sulphate led to the formula $U(SO_4)_2,3{\cdot}26H_2O$.

The solid solutions were prepared by dissolving weighed amounts of uranous sulphate and of thorium nitrate in dilute nitric acid and adding freshly distilled ammonia water. The co-precipitated hydroxides were centrifuged and washed with water distilled in quartz. Evaporation of the supernatant liquids to dryness in a weighed platinum crucible confirmed that precipitation was complete. The hydroxides were made into a sludge in a platinum boat and dried in a copper furnace at 70° in a stream of hydrogen. The fluorination was carried out in the same furnace in a stream of hydrogen fluoride and hydrogen at 500°.

Table I.

	Impurities (p.p.m.)				
Compound	Fe	Co	Ni	Cr	Mn
Uranyl sulphate	20	<4	<4	<20	<4
Thorium nitrate	<20	<10	<10	<50	<2
Uranous sulphate	20	<8	< 8	<40	<8
$U_{0{\cdot}62}Th_{0{\cdot}38}F_4$	<10	<10	10	<50	<2

* Part IV, *J.*, 1951, 2047.

Spectrographic analyses of the materials for possible ferromagnetic contamination at various stages during the preparation are given in Table I. Magnetic measurements were restricted to one field strength only, but these amounts of ferromagnetic impurities should make only an extremely small contribution to the observed susceptibilities. The measurements were made on 2—10-mg. samples, the magnetic susceptibility balance described by Dawson and Lister (*J.*, 1950, 2177) being used. Two separate preparations were made at each dilution studied, and several samples were taken from each for the measurement of susceptibility at room temperature. The agreement was in general quite close, but there were rather wide variations in the dilute uranium solid solutions since, for instance, an error of only 0·5% on the actual measurements leads to an error of 10% in the deduced susceptibility of the U(IV) ion at 5% uranium content. The results over the temperature range 90—350° K. are given in Table II, the uranium and thorium contents being expressed as atomic percentages. Table III gives the Weiss constants of the solid solutions, obtained by plotting the reciprocal of $\chi_{U(IV)}$ against temperature, and also the effective magnetic moments calculated from the formula $\mu = 2{\cdot}83\sqrt{\chi_{U(IV)} \cdot (T + \Delta)}$.

TABLE II.

Composition, %	T, °K.	$10^6\chi_g$.	$10^6\chi_m$.	$10^6\chi_{U(IV)}$	Composition, %	T, °K.	$10^6\chi_g$.	$10^6\chi_m$.	$10^6\chi_{U(IV)}$
U, 100	90	22·39	7030	7,091	U, 25	90	10·26	3177	12,950
	197	14·61	4588	4,649	Th, 75	199	5·94	1839	7,579
	300	10·67	3530	3,411		300	4·24	1314	5,497
	332	9·92	3117	3,176		328	3·76	1165	4,901
U, 90	90	22·27	6982	7,825	U, 11	90	5·66	1748	16,430
Th, 10	200	13·41	4207	4,742	Th, 89	200	2·822	871·2	8,475
	301	10·01	3139	3,560		303	1·837	567·0	5,701
	334	9·21	2888	3,277		355	1·579	487·5	4,979
U, 75	90	20·60	6440	8,668	U, 5·3	90	2·903	895·6	18,040
Th, 25	199	12·60	3940	5,334	Th, 94·7 ...	199	1·437	443·3	9,501
	295	9·22	2881	3,922		300	0·936	288·8	6,586
	328	8·47	2650	3,610		330·5	0·814	251·1	5,874
U, 50	90	16·92	5261	10,640					
Th, 50	200	10·11	3144	6,409					
	298	7·38	2296	4,713					
	334	6·62	2060	4,241					

χ_g = Gram-susceptibility.
χ_m = Molar-susceptibility.

TABLE III.

U, %	100	90	75	50	25	11	5·3
Δ	102	90	80	68	55	22	25
μ	3·30	3·34	3·43	3·68	3·93	3·86	4·12

Samples of pure thorium tetrafluoride were prepared by the same method and gave a molar diamagnetic susceptibility of 59×10^{-6}. This is very close to the theoretical value calculated by Angus's method, 60×10^{-6} (*Proc. Roy. Soc.*, 1932, *A*, **136**, 569), which was taken as the diamagnetic correction for 100% ThF_4. The value 61×10^{-6}, calculated by the same method, was taken as the diamagnetic correction for 100% UF_4.

DISCUSSION.

The values of the susceptibility of uranium tetrafluoride in Table II are a little higher than those already reported by the author (*loc. cit.*). This is believed to be due to a small amount of UO_2F_2 in the commercial sample used previously. This had some effect on the Weiss constant but the deduced magnetic moments are essentially the same—3·28 previously and 3·30 in the present communication. This is also in agreement with the value 3·30 reported by Elliott (*Physical Rev.*, 1949, **76**, 431), who gives the somewhat higher Weiss constant of 147°, however.

The solid solutions all obey the Weiss–Curie law over the temperature range studied, and the values of the Weiss constant, the effective magnetic moment, and the susceptibility of U(IV) at 300° K. are plotted against composition in Fig. 1. Their behaviour is different from that observed in the oxide solid-solution system as shown in Fig. 2.

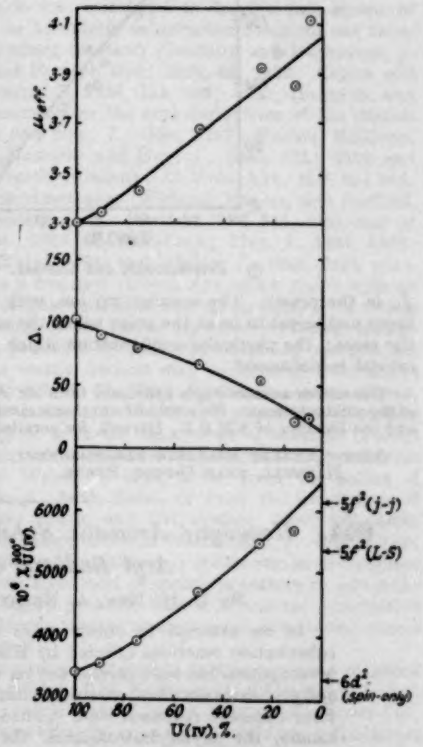
Trzebiatowski and Selwood (*loc. cit.*) obtained their oxide solid solutions by co-precipitating ammonium diuranate and thorium hydroxide, followed by simultaneous ignition and reduction at 1200° in hydrogen. The present author in collaboration with Dr. M. W. Lister obtained results on the same system starting from the mechanically mixed oxides which were compressed into pellets and made homogeneous by ignition to about 2400° in a vacuum furnace. The agreement with Trzebiatowski and Selwood's results is good, and the two sets taken together show that the moment of the U(IV) ion is definitely dependent on concentration, the value falling from 3·20 in 100% UO_2 to about 3·0 Bohr magnetons at infinite dilution.

On the other hand, in the fluoride solid solution system the effective moment of the U(IV) ion rises from 3·30 in 100% UF_4 to about 4·05 at infinite dilution. The possible theoretical values which may be obtained by using Hund's formula, $\mu = g\sqrt{J(J+1)}$ are:

Electronic configuration	Ground state	Effective moment: *L–S* coupling	*j–j* coupling	spin only
$5f^2$	$^3H_4$	3·58	3·84	2·83
$6d^2$	$^3F_2$	1·63	1·96	2·83

Thus it appears that at infinite dilution the magnetic moment is close to the theoretical value for two 5*f*-shell electrons in *j–j* coupling. This point is brought out even more clearly from a consideration of the susceptibility curve where the complication due to the inclusion of a Δ value does not arise. At infinite dilution, the extrapolated susceptibility of U(IV) at 300° K. is about 6360 × 10^{-6}, the theoretical value for a $5f^2$ configuration in *j–j* coupling being 6140 × 10^{-6}, compared with the theoretical values of 5390 × 10^{-6} and 3330 × 10^{-6} for a $5f^2$ configuration in *L–S* coupling and the spin-only value to be expected from a $6d^2$ configuration, respectively (in the oxide system, the extrapolated susceptibility is about 3550 × 10^{-6} in agreement with the "spin-only" value). At 90° K., the extrapolated suceptibility at infinite dilution is equal, within the limits of experimental error, to the theoretical value of 20,500 × 10^{-6} calculated for a $5f^2$ configuration with *j–j* coupling (the "spin-only" value being 11,100 × 10^{-6} at this temperature).

FIG. 1.
UF_4–ThF_4. *Solid solutions.*



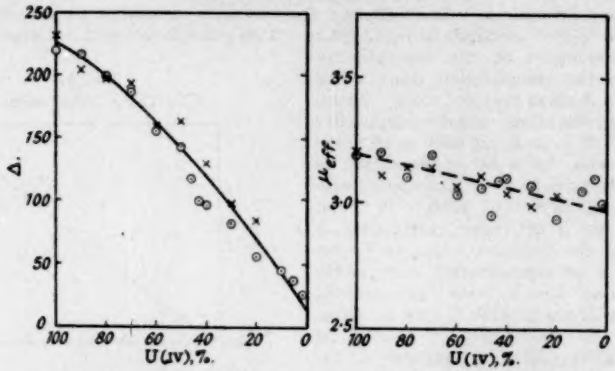
It appears that there is no correlation of the observed magnetic effects in this sytem with the presence of two unpaired electrons in the 6*d* level in the uranous ion. On the other hand, there is definite evidence in favour of the two electrons occupying the 5*f* level and having *j–j* coupling. The theoretical susceptibility for the *L–S* type of coupling is somewhat lower than the *j–j* value (see above), but consideration of the low iron content of the materials (Table I), together with the fact that the thorium fluoride is diamagnetic, indicates that the agreement with the susceptibilities derived on the assumption of *j–j* coupling is probably real and not due to an additional contribution to the susceptibility from ferromagnetic impurities.

It is usually assumed that electrons occupying the 5*f* level will be less effectively shielded from external interaction than is the case with 4*f* electrons. This probably accounts for the change in the Weiss constant as UF_4 is diluted with ThF_4. The change is intermediate between that observed by Selwood for the system Nd_2O_3–La_2O_3, Δ = 59° at 100% Nd_2O_3 to Δ = 30° at 2% Nd_2O_3 (*J. Amer. Chem. Soc.*, 1933, **55**, 3161) and that observed in the UO_2–ThO_2 system (Fig. 2), Δ = 232° at 100% UO_2 to Δ = 26° at 2% UO_2, *i.e.*, intermediate between the well-shielded 4*f*-shell type and the unshielded 6*d*-shell type. The value of the Weiss constant extrapolated to infinite dilution does not appear to be zero, but this is not inconsistent with the *f*-like nature of the unpaired electrons, since the 4*f* electrons in the Nd_2O_3–La_2O_3 system also give rise to a small positive Δ value at infinite dilution owing to the effects of the crystalline field of the diamagnetic diluent atoms.

In the elements beyond actinium, there is increasing evidence from magnetic data that thorium compounds have " unpaired " electrons in the 6*d* level; for instance, ThS is diamagnetic (Brewer *et. al., J. Amer. Chem. Soc.*, 1950, **72**, 4019), and the present author has found that ThSe has a small temperature-independent paramagnetism, these facts indicating very strong exchange coupling between (presumably) unshielded electrons. On the other hand, the plutonium tervalent ion has a $5f^5$ electron configuration (Dawson, Mandleberg, and Davies,

FIG. 2.

UO_2–ThO_2. *Solid solutions.*



○ *Trzebiatowski and Selwood.* × *Dawson and Lister.*

J., in the press). The uranium(IV) ion, with two unpaired electrons, lies between these two types and seems to be at the point where the energies of the 6*d* and 5*f* levels are approximately the same; the particular configuration which the ion assumes then appears to depend on the crystal environment.

The author acknowledges assistance from Mr. A. E. Truswell and Mr. D. Davies in the preparation of the solid solutions. He would like to thank members of the Spectrographic Section for their analyses, and the Director of A.E.R.E., Harwell, for permission to publish these results.

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644. *Homolytic Aromatic Substitution. Part I. The Action of Aryl Radicals on Nitrobenzene.*

By D. H. HEY, A. NECHVATAL, and T. S. ROBINSON.

In an attempt to obtain more accurate quantitative information on substitution reactions effected by free radicals and atoms, an experimental investigation has been carried out on the extent of substitution at the *o*-, *m*-, and *p*-positions in nitrobenzene by phenyl, *p*-bromophenyl, and *p*-tolyl radicals. Four different reactions were studied, namely, those of the sodium aryldiazoate, the acylarylnitrosamine, the 1-aryl-3 : 3-dimethyltriazen, and the acyl peroxide, and the percentage of substitution at the *m*-position was found to be of the order of 12% for *p*-bromophenyl and 9% for *p*-tolyl, which figures were independent of the particular reaction used. The products were analysed both by a bromometric method on the mixture of bases obtained on reduction and by means of infra-red spectroscopy. The two methods showed excellent agreement and the results substantiate the theoretical views originally proposed by one of us in 1934.

INVESTIGATIONS on the arylation of aromatic compounds by the action of certain diazo-compounds and the peroxides of aromatic acids revealed a series of reactions in which the normal directive influence of substituent atoms or groups was not operative (Grieve and Hey, *J.*, 1934,

1797; Hey, *ibid.*, p. 1966). In order to explain the course of these reactions it was suggested that the substituting agent was an electrically neutral free aryl radical of short life, the reactions of which would not be subject to the electrical charges which are responsible for the position taken up by the entering group in, for example, nitration or sulphonation. Such reactions have been referred to as "amphoteric aromatic substitution" because the entering group behaved as if it were either electrophilic (cationoid) or nucleophilic (anionoid) in type, as "invariable *ortho-para* substitution" because in all the reactions studied the main and often the sole products isolated were the *o*- and *p*-isomerides, irrespective of the nature of the substituent atom or group present, and also as "radical substitution" (Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900). Many further examples of this type of aromatic substitution have now come to light, and it appears more logical to classify such reactions as "homolytic substitution" reactions in order to distinguish them from the better-known reactions involving electrophilic or nucleophilic reagents which may be termed "heterolytic substitution" reactions.

Among aromatic substitution reactions which are considered to involve free atoms or radicals and which may therefore be classified as homolytic substitution reactions are those of (*a*) the diazoic acids or the diazoates (the Gomberg reaction) (Gomberg and Bachmann, *J. Amer. Chem. Soc.*, 1924, **46**, 2339; Gomberg and Pernert, *ibid.*, 1926, **48**, 1372; Grieve and Hey, *J.*, 1938, 108; Heilbron, Hey, and Wilkinson, *J.*, 1938, 113, 699; Elks, Haworth, and Hey, *J.*, 1940, 1284, etc.), (*b*) the acylarylnitrosamines or the acyl derivatives of the diazoic acids (Bamberger, *Ber.*, 1897, **30**, 366; Grieve and Hey, *J.*, 1934, 1797; France, Heilbron, and Hey, *J.*, 1938, 1364; 1939, 1283, 1288; Haworth and Hey, *J.*, 1940, 361; Hey and Lawton, *J.*, 1940, 374, etc.), (*c*) the 1-aryl-3 : 3-dimethyltriazens (I.G. Farb. Akt., B.P. 513,846; Elks and Hey, *J.*, 1943, 441), (*d*) the arylazotriarylmethanes (Wieland, Popper, and Seefried, *Ber.*, 1922, **55**, 1816; Hey, *J.*, 1934, 1966; Wieland *et al.*, *Annalen*, 1934, **514**, 145), and (*e*) the acyl peroxides (Gelissen and Hermanns, *Ber.*, 1925, **58**, 285 *et seq.*; Hey, *J.*, 1934, 1966; Wieland, Ploetz, and Indest, *Annalen*, 1937, **532**, 166; Hey and Walker, *J.*, 1948, 2213, etc.). All these reactions are considered to give rise to a free aryl radical, Ar·, which reacts with an aromatic compound C_6H_5R to give a mixture of unsymmetrical diaryls $Ar{\cdot}C_6H_4{\cdot}R$, in which the *o*- and *p*-isomerides predominate. In addition to the above arylation processes, further examples of homolytic substitution have been provided by reactions involving methylation and hydroxylation. In the former process the methyl radical may be derived from acetyl peroxide (Fieser and Oxford, *J. Amer. Chem. Soc.*, 1942, **64**, 2060), lead tetra-acetate (Fieser, Clapp, and Daudt, *ibid.*, p. 2052; Fieser and Chang, *ibid.*, p. 2043), phenyl iodosoacetate (Sandin and McCormack, *ibid.*, 1945, **67**, 2051), or from the electrolysis of acetates (Fieser, Clapp, and Daudt, *loc. cit.*), while in the latter the hydroxyl radical may originate from a ferrous salt and hydrogen peroxide (Loebl, Stein, and Weiss, *J.*, 1949, 2074), from the action of ionising radiations on aqueous solutions (*idem*, *J.*, 1950, 2704), or from the irradiation of aqueous solutions of ion-pair complexes (Bates, Evans, and Uri, *Nature*, 1950, **166**, 869). Evidence has also recently been brought forward (Klapproth and Westheimer, *J. Amer. Chem. Soc.*, 1950, **72**, 4461) which indicates that aromatic mercuration may follow one of two courses according to whether mercuric perchlorate in perchloric acid or mercuric acetate in non-polar solvents is used. In the latter case it seems highly probable that a homolytic substitution process is largely involved, whereas under the former conditions the normal orientation effects of an electrophilic substitution process are observed.

An alternative hypothesis for the arylation process applicable to the reactions of alkali diazoates and acylarylnitrosamines has been put forward by Hodgson (*J.*, 1948, 348; *J. Soc. Dyers Col.*, 1948, **64**, 99; 1949, **65**, 347; cf. Hey and Waters, *J.*, 1948, 882; *J. Soc. Dyers Col.*, 1948, **64**, 359), who considers that in these reactions nitrogen must be evolved from a diazonium ion, thus giving rise to an aryl cation and not a neutral free radical. The aryl cation is considered to react at the *o*- and *p*-positions to the nitro-group in nitrobenzene, which by solvent effects is converted into a quinonoid form showing anionoid reactivity at these positions, thus revealing why the *m*-position should not be attacked. Such a mechanism is not supported by the present investigation.

The absence of accurate quantitative data with regard both to orientation and to the activation or deactivation of the nucleus by the presence of substituent atoms or groups has hitherto made any comprehensive theoretical interpretation of the substitution reactions of free radicals and atoms highly speculative. The present communication is the first of a series designed to provide an adequate quantitative background to the general problem.

If the substituent atom or group R in $C_6H_5{\cdot}R$ exerts no influence at all on the position

taken up by an entering atom or group, the distribution of isomerides would be represented by 40% *o*-, 40% *m*-, and 20% *p*-. It will therefore be convenient to represent any disturbance of this ratio by the presence of the substituent R by classifying R as *op*-directing if the proportion of the *m*-isomeride is less than 40%, and as *m*-directing if it exceeds 40%. In electrophilic and nucleophilic substitution reactions the ease of reaction at any position in an aromatic nucleus is largely controlled by the net electric charge at that point. If the substituting agent is electrically neutral, it might be inferred that all the available nuclear positions are equally favoured, but the completion of the reaction requires the provision of an odd electron which has to be paired with the odd electron provided by the free radical, and the ease with which such an electron can be made available may be significantly different at the various positions.

The first example reported of the isolation of all three isomerides in a homolytic arylation process referred to reactions with ethyl benzoate (R = CO_2Et) (Hey, *J.*, 1934, 1966), and, later, the careful fractionation of the products of the reaction between 4-nitrosoacetamidodiphenyl and (*a*) chlorobenzene, (*b*) bromobenzene, and (*c*) toluene (France, Heilbron, and Hey, *J.*, 1938, 1364; 1939, 1283) gave all three isomeric *p*-terphenyls in the proportions shown below:

R in $C_6H_5 \cdot R$	Yield of isomerides *p*-Ph·$C_6H_4 \cdot C_6H_4 \cdot R$, %		
	ortho-	*meta*-	*para*-
Cl	32	20	48
Br	33	15	52
Me	50	6	44

Such figures, which represent percentages based on the total terphenyl isolated, can be accepted as no more than rough approximations, but they give an unmistakable indication that in these reactions the group R is predominantly *op*-directive in character. For the substitution reactions of nitrobenzene (R = NO_2) more accurate figures have recently been provided by Loebl, Stein, and Weiss (*locc. cit.*), who have investigated the action of hydroxyl radicals, using saturated aqueous solutions of nitrobenzene and (*a*) the ferrous sulphate–hydrogen peroxide reaction (Fenton's reagent) and (*b*) ionising radiations. Analysis of the mixture of isomeric nitrophenols gave the following figures, which for the ionising radiation experiments were claimed to have an accuracy of $\pm 5\%$ for the *o*- and $\pm 10\%$ for the *m*- and *p*-values:

Source of hydroxyl radical	pH	Yield of isomeric nitrophenols, %		
		ortho-	*meta*-	*para*-
Fenton's reagent	—	25—30	20—25	50—55
$H_2O \rightsquigarrow H\cdot + OH\cdot$	2	34·5	31	34·5
"	6	35·5	29	35·5
"	12	27·5	27	45·5

The above figures again show that in these reactions the nitro-group, like methyl and the halogens, belongs to the *op*-directing type, as in fact had been indicated in the earlier qualitative work on the arylation processes.

The Arylation of Nitrobenzene.—The present communication describes the quantitative results which have been obtained on the arylation of nitrobenzene. Use has been made of four different reactions as the source of the aryl radical, namely, (*a*) the diazoate, (*b*) the acylarylnitrosamine, (*c*) the 1-aryl-3 : 3-dimethyltriazen, and (*d*) the acyl peroxide, and the resulting mixture of nitrodiphenyls was reduced and submitted to a bromometric titration by means of a mixture of potassium bromide and potassium bromate in aqueous acid. Arylation at the *m*-position with regard to the nitro-group will give rise on reduction to a 3-aminodiphenyl which will require three molecules of bromine, whereas arylation at the *o*- and *p*-positions will give 2- and 4-aminodiphenyls, which will require only two molecules of bromine. Thus the bromometric titration can give the ratio $m : (o + p)$. Preliminary experiments on the analytical method showed that 4-aminodiphenyl itself could not be brominated quantitatively by this method (R. E. Parker, unpublished results), presumably owing to the occurrence of oxidation involving the 4′-position. It was found, however, that when the hydrogen atom at the 4-position was replaced by a bromine atom or a methyl group no such difficulty arose and accordingly the aryl radicals chosen for use in this method were *p*-bromophenyl and *p*-tolyl. The 2-, 3-, and 4-amino-4′-methyldiphenyls and the 2-, 3- and 4-amino-4′-bromodiphenyls were all shown to behave normally on bromometric titration. The detailed experimental procedure developed for these determinations is described below, and its reliability for the purpose in hand was rigorously tested by means of determinations on synthetic mixtures of known composition.

The results obtained in this way show that when the entering radical is *p*-bromophenyl the percentage substitution at the *m*-position with respect to the nitro-group is of the order of 12%, whereas for the *p*-tolyl radical the corresponding figure is 9%, as indicated in Table I (p. 2902).

These results again show that the nitro-group is predominantly *op*-directing in character in these reactions but that some reaction takes place at all three positions in the nucleus, an observation which had not previously been established experimentally, either quantitatively or qualitatively, in an arylation process. It is also revealed that the ratio of *m*- to *op*-substitution is substantially independent of the source from which the aryl radical is derived, which observation gives strong confirmation of the view that there is one mechanism common to all

FIG. 1.

Nitrodiphenyls in Nujol mull.

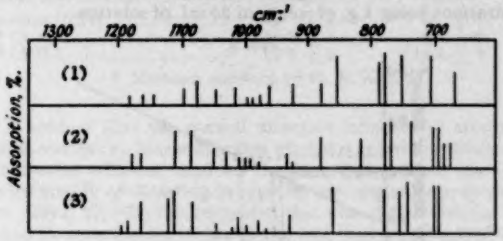
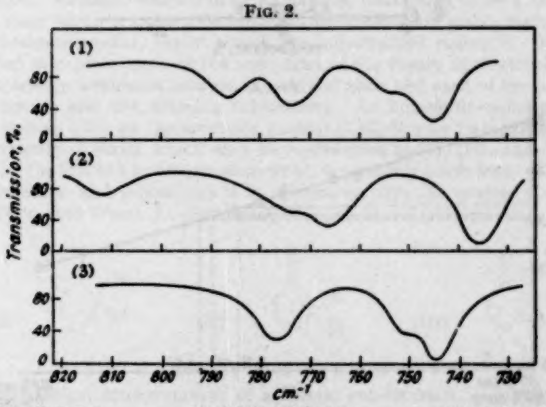


FIG. 2.



(1) 2-*Nitrodiphenyl.* (2) 3-*Nitrodiphenyl.* (3) 4-*Nitrodiphenyl.*

four reactions. The anomalous figures shown for the reactions carried out with 1-*p*-bromophenyl-3 : 3-dimethyltriazen have been shown to be due to the fact that in the decomposition of the triazen with dry hydrogen chloride some of the *p*-bromobenzenediazochloride rearranges to *p*-chlorobenzenediazobromide, the extent of the conversion depending on the time of the reaction. Such interchange reactions have been reported previously by Hantzsch and Smythe (*Ber.*, 1900, **33**, 505). A further example of such rearrangement was encountered during the attempted preparation of 2-nitrodiphenyl by the interaction of 1-*o*-nitrophenyl-3 : 3-dimethyltriazen and boiling benzene in the presence of dry hydrogen chloride. The sole diaryl isolated as the product of this reaction was 2-chlorodiphenyl, which indicates an apparently complete conversion of *o*-nitrobenzenediazochloride into *o*-chlorobenzenediazonitrite before the diazo-compound decomposes (cf. Meldola and Eyre, *J.*, 1902, **81**, 988).

In order further to confirm the existence of substitution at the *m*-position with regard to the nitro-group, a reaction was carried out between benzoyl peroxide and nitrobenzene, and the resulting mixture of nitrodiphenyls was subjected to careful fractional crystallisation. In

addition to 2- and 4-nitrodiphenyl, 3-nitrodiphenyl was isolated and identified by a mixed melting point.

Analysis of the Isomeric Nitrodiphenyl Mixtures by Infra-red Absorption Spectroscopy.—The reliability of the bromometric technique for the analysis of the mixtures of isomeric nitrodiphenyls outlined above was substantiated by the application of infra-red absorption spectroscopy which, in addition, gave the individual proportions of all three isomers present with the unsubstituted phenyl radical as the substituting agent. A preliminary study of the infra-red absorption spectra taken in a Nujol mull of 2-, 3-, and 4-nitrodiphenyl in the crystalline state showed that the strongest characteristic bands for each isomer are in the region 660—900 cm.$^{-1}$ (Fig. 1). A suitable solvent covering this region is nitromethane (Nielsen and Smith, *Ind. Eng. Chem.*, 1943, **15**, 609) and the spectrum of the available nitromethane (B.D.H.) showed that a clear region extended only from about 700 to 800 cm.$^{-1}$. Spectra in the region 710—810 cm.$^{-1}$ of solutions of each of the three isomers in nitromethane are presented in Fig. 2, the solution concentrations being 1 g. of solute in 25 ml. of solution.

FIG. 3.

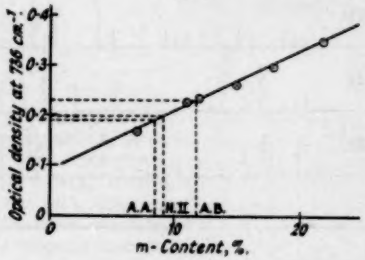
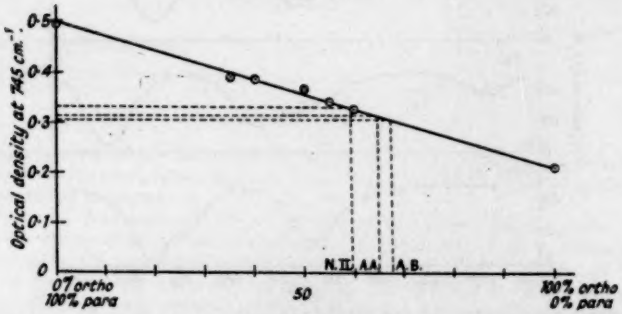


FIG. 4.



There is considerable overlapping in the characteristic absorption bands of the three isomers, and a quantitative analysis of solutions of an unknown mixture based on measurements of the absorption of solutions of the pure isomers could not be expected to give sufficient accuracy. Accordingly, a family of solutions of the three isomers was prepared, each containing a known fraction of the 2-, 3-, and 4-nitrodiphenyl such that the total nitrodiphenyl content was always 1 g. in 25 ml. of solution. In attempting to match these synthetic isomeric mixtures with one of the unknown mixtures it became clear that the *m*-content of the latter was about 10% and that the absorption at 736 cm.$^{-1}$ was a direct measure of the amount of this isomer present. The graph (Fig. 3) shows the variation of optical density at 736 cm.$^{-1}$ with *m*-content of various members of this family of solutions of synthetic mixtures. The optical densities at 736 cm.$^{-1}$, due to the pure *o*- and *p*-compounds are 0·036 and 0·063, respectively, and it has been shown that for the particular points on this graph the variation in optical density, due to change in *o*- and *p*-content, is less than 0·005, *i.e.*, less than one-thirtieth of the optical density due to the *m*-isomer. All the measurements were made in the same cell of thickness about 130 μ.

After the *m*-content had been estimated in this way, the *o*- and the *p*-proportion were obtained

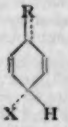
by measurement of optical density at 745 cm.$^{-1}$, which is sensitive to the *o* : *p*-ratio. As the absorption with the original solutions gave rather high optical densities, these measurements were carried out in solutions at one-third of the initial concentrations, *i.e.*, with 1 g. in 75 ml. of solution. In Fig. 4 a graph is shown giving the observed optical densities of the pure *o*- and *p*-isomers and of mixtures of the two. The latter were actually estimated from measurements on the original family of synthetic mixtures, after dilution to one-third of the original concentration and allowance for the extra dilution due to the small amount of *m*-isomer present. From this graph the *o* : *p*-ratio of the unknown mixtures was estimated.

The results obtained by means of the above procedure are given below :

Source of phenyl radical	Percentage composition of the mixture of isomeric nitrodiphenyls : *ortho-*	*meta-*	*para-*
Sodium benzenediazoate (N.II)	54 ± 4	9 ± 2	37 ± 4
Benzoyl peroxide * (A.A.)	59·5 ± 4	8·5 ± 2	32 ± 4
Benzoyl peroxide * (A.B.)	59·5 ± 4	11·5 ± 2	29 ± 4

* Mixtures supplied by D. R. Augood.

Discussion.—It is evident that the normal directive influence of atoms or groups already present in the aromatic nucleus no longer operates when the entering substituent is a free radical. The available experimental evidence confirms the fact that in such reactions all substituent atoms or groups are invariably *op*-directing in type, as was originally proposed in 1934. Waters (*Trans. Faraday Soc.*, 1941, **37**, 772) has suggested that one of the essential differences between homolytic and heterolytic substitution is due to the fact that an attacking ion or polar reagent perturbs the aromatic molecule when still at a distance, converting it by a tautomeric change into a transition state which is quite different from the mesomeric stable state, whereas a free-radical reagent, being non-polar, would attack the unperturbed molecule. Waters (*J.*, 1948, 727) has attempted to explain some of the anomalies of the theory of electrophilic substitution by estimating the energy difference between the normal state and each of the possible transition states of the molecule and the entering substituent. In homolytic substitution the initial attack by a free radical (X•) on the aromatic nucleus $C_6H_5{\cdot}R$ may be regarded as an addition reaction to give transition states which may be represented as (I), (II), and (III), which then achieve stability by the loss of a hydrogen atom which is probably never free. The predominance of substitution at the *o*- and *p*-positions is in agreement with the greater stability of (I) and (III) (cf. Loebl, Stein, and Weiss, *J.*, 1949, 2075).

(I) (II) (III) 

A quantum-mechanical interpretation of aromatic substitution by means of free radicals has been provided by Wheland (*J. Amer. Chem. Soc.*, 1942, **64**, 900), who used a molecular-orbital method which also embraces within its treatment substitution reactions by electrophilic and nucleophilic reagents. In the case of radical substitution, one electron is required which with the odd electron provided by the radical can form a new covalent bond in the activated complex formed between the nucleus and the substituting agent. The energy (ΔW) required to perturb the stable structure of the aromatic compound so as to produce an odd electron at the various positions in the nucleus was calculated, and these energies are regarded as the controlling factors governing the reactivity of the various positions in the nucleus. The greater the value of ΔW for any particular position in the nucleus, the less energetically favoured is that particular transition state, and therefore that position will be relatively less reactive towards the approaching radical.

These calculations show that all substituents activate mainly the *o*- and *p*-positions, but that some *m*-substitution should be expected in all reactions, although only as a minor constituent. Calculations which lead to a similar conclusion with regard to free-radical substitution have been made by Coulson (*J. Chim. physique*, 1949, **45**, 243; *Research*, 1951, **4**, 307; and personal communications), making use of the concept of free valence.

Addendum.—After this paper was written DeTar and Scheifele (*J. Amer. Chem. Soc.*, 1951, **73**, 1442) published the results of their investigation on the orienting influence of the nitro-group in the formation of nitrodiphenyls by the reaction of nitrobenzene with nitrosoacetanilide, with benzoyl peroxide, and with benzenediazonium chloride and alkali. The mixture of nitrodiphenyls was determined by an ultra-violet spectroscopic method and it was shown that the nitro-group was largely *op*-directing but gave rise to the formation of a small proportion of the *m*-isomer. These results are in substantial agreement with those reported above.

Experimental.

(All m.p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.)

Preparation of Reference Compounds.—*4-Bromo-4'-nitrodiphenyl.* 4-Nitrodiphenyl was treated with bromine in acetic acid at 100° as described by Le Fèvre and Turner (*J.*, 1926, 2041). 4-Bromo-4'-nitrodiphenyl crystallised from acetic acid in colourless needles, m. p. 172·5°. Le Fèvre and Turner record m. p. 170—172°.

4-Bromo-3'-nitrodiphenyl. 3-Nitrodiphenyl, prepared from *m*-nitrobenzoyl peroxide and benzene (Hey and Walker, *J.*, 1948, 2217), was brominated as described by Blakey and Scarborough (*J.*, 1927, 3000). 4-Bromo-3'-nitrodiphenyl was obtained in light brown plates, m. p. 94° after crystallisation from ethanol. Blakey and Scarborough record m. p. 95°.

4-Bromo-2'-nitrodiphenyl. 2-Nitrodiphenyl (9 g.) was stirred with bromine (3·2 ml.), anhydrous ferric chloride (0·5 g.), and water (25 ml.) for 5 hours at room temperature (cf. Le Fèvre and Turner, *loc. cit.*). After being kept overnight at room temperature the mixture was stirred with excess of aqueous sodium carbonate and the resulting oil was extracted with ether, the ethereal extract washed (aqueous sodium carbonate) and dried (K_2CO_3), and the ether evaporated. The resulting oil was dissolved in ethanol and cooled to −80°. The crude 4-bromo-2'-nitrodiphenyl which separated crystallised from ethanol in pale yellow plates, m. p. 64° (1 g.). Schultz, Schmidt, and Strasser (*Annalen*, 1881, **107**, 351) record m. p. 65°. Attempts to increase the yield of 4-bromo-2'-nitrodiphenyl by brominating 2-nitrodiphenyl at higher temperatures, both in the absence and in the presence of acetic acid and ferric chloride failed, the main product consisting of an oil from which only about 10% of 4-bromo-2'-nitrodiphenyl could be isolated. The more vigorous brominations at 100° in the presence of ferric chloride resulted in the production of a *dibromo-2-nitrodiphenyl* (*ca.* 20%), which crystallised from ethanol in light brown prisms, m. p. 131—131·5° (Found: C, 40·1; H, 1·8. $C_{12}H_7O_2NBr_2$ requires C, 40·3; H, 2·0%).

2-, 3-, and 4-Amino-4'-bromodiphenyl hydrochlorides. The three isomeric amino-4'-bromodiphenyl hydrochlorides were prepared from the 4'-bromonitrodiphenyls by reduction in ethanolic solution with stannous chloride and concentrated hydrochloric acid. The bases were extracted with ether from the reaction products which had been made strongly alkaline, and the ethereal solutions were dried (K_2CO_3). Passage of a stream of dry hydrogen chloride through the ethereal solutions precipitated the base hydrochlorides, which were separated by filtration, washed well with dry ether, and kept in a vacuum for 12 hours before use.

4-Methyl-4'-nitrodiphenyl. 4-Methyldiphenyl (Gomberg and Pernert, *J. Amer. Chem. Soc.*, 1926, **48**, 1373) was nitrated by the method of Grieve and Hey (*J.*, 1932, 1888). 4-Methyl-4'-nitrodiphenyl separated from ethanol, and had m. p. 140°. Grieve and Hey record m. p. 140°.

4-Methyl-3'-nitrodiphenyl. (*a*) A suspension of 4-acetamido-4'-methyldiphenyl (2·5 g.) in a mixture of acetic acid (25 ml.) and concentrated sulphuric acid (4 ml.) was well-stirred at 30° during the addition of a mixture of fuming nitric acid (2 ml.) and concentrated sulphuric acid (1·5 ml.). The resulting brown solution was kept at 30° for 2 hours and then poured on ice. The yellow precipitate was filtered off and washed with water. The crude *4-acetamido-4'-methyl-3-nitrodiphenyl* crystallised from ethanol in yellow needles, m. p. 162·5—163° (2·1 g.). Crystallisation from light petroleum (b. p. 40—60°)–benzene gave pale yellow needles, m. p. 165·5—166° (Found: C, 66·9; H, 4·8; N, 10·2. $C_{14}H_{14}O_3N_2$ requires C, 66·65; H, 5·2; N, 10·4%). 4-Acetamido-4'-methyl-3-nitrodiphenyl (2·0 g.) was boiled under reflux with 70% sulphuric acid (50 ml.) for 1 hour. A small portion of the resulting colourless suspension was made alkaline with aqueous sodium hydroxide, and the *4-amino-4'-methyl-3-nitrodiphenyl* thus obtained was collected, and crystallisation from ethanol and then from light petroleum (b. p. 60—80°)–benzene gave bright red prisms, m. p. 186·5—187° (Found: C, 68·4; H, 5·3; N, 12·1. $C_{13}H_{12}O_2N_2$ requires C, 68·45; H, 5·3; N, 12·3%). The main bulk of the colourless suspension of 4-amino-4'-methyl-3-nitrodiphenyl sulphate was mixed with 50% sulphuric acid (10 ml.) and cooled to 0°, and the stirred suspension diazotised with excess of aqueous sodium nitrite. The diazonium solution was added to cold aqueous hypophosphorous acid which had been prepared by adding concentrated sulphuric acid (20 ml.) to an ice-cold, well-stirred suspension of calcium hypophosphite (60 g.) in water (60 ml.) and filtering off the calcium sulphate. The mixture of diazonium solution and hypophosphorous acid was kept at 0° for 2 days and then extracted with ether. Evaporation left *4-methyl-3'-nitrodiphenyl*, m. p. 65—74° (0·91 g.), which crystallised from ethanol and then from light petroleum (b. p. 40—60°) in pale yellow plates, m. p. 77·5° (Found: C, 73·35; H, 5·2; N, 6·4. $C_{13}H_{11}O_2N$ requires C, 73·25; H, 5·2; N, 6·6%).

(*b*) The interaction of diazotised *m*-nitroaniline and toluene in the presence of sodium acetate provides confirmation for earlier observations (France, Heilbron, and Hey, *J.*, 1938, 1283) of the predominant *o*-directing property of the methyl group in reactions of this type, and for this reason the reaction did not constitute a satisfactory route to 4-methyl-3'-nitrodiphenyl. *m*-Nitroaniline (70 g.), suspended in

concentrated hydrochloric acid (160 ml.), was diazotised at 0° by slow addition of a solution of sodium nitrite (40 g.) in water (60 ml.). A solution of sodium acetate (88 g. of the hydrated salt) in water (200 ml.) was added to a well-stirred, cooled mixture of the diazonium solution and toluene (1 l.), and the reaction mixture was left at room temperature for 12 hours and then heated to 60—70° for a further 12 hours before the dark brown toluene layer was separated, washed (aqueous sodium hydroxide), and dried ($CaCl_2$). The residual aqueous emulsion was continuously extracted with benzene for 16 hours and this extract was added to the dry toluene solution. Removal of the solvents left a dark tar, which on distillation gave (i) a yellow oil (9·6 g.), b. p. 40—120°/0·07 mm., (ii) a yellow oil (31·9 g.), b. p. 120—129°/0·07 mm., and (iii) a brown oil (15·4 g.), b. p. 129—164°/0·07 mm. Fractions (ii) and (iii) deposited *2-methyl-3′-nitrodiphenyl* (20·3 g.), which crystallised from ethanol and then from light petroleum (b. p. 40—60°) in yellow needles, m. p. 72·5—73° (Found: C, 72·8; H, 5·05; N, 6·2. $C_{13}H_{11}O_2N$ requires C, 73·25; H, 5·2; N, 6·6%).

From the oils which remained after the separation of the main product, several crops of mixed crystals, m. p. 30—50°, and *m*-dinitrobenzene, m. p. 89—90°, separated. The crops of mixed crystals were bulked (4·35 g.), dissolved in light petroleum (b. p. 40—60°) (100 ml.), and allowed to percolate through a column (90 × 3 cm.) packed with alumina (200 g.; B.D.H. " For chromatographic analysis " grade) which had previously been heated to about 400°. The column was eluted with ten successive portions of benzene–light petroleum (b. p. 60—80°) mixtures ranging from 10% benzene–90% light petroleum to 50% benzene–50% light petroleum. The residues from fractions 3 and 4, after crystallisation from light petroleum (b. p. 40—60°), gave 2-methyl-3′-nitrodiphenyl in white needles, m. p. 72° both alone and when mixed with the main product of this reaction (m. p. 72·5°). The residues from fractions 5, 6, and 7 consisted of mixed crystals, m. p. 54—58°, and the residues from fractions 8, 9, and 10, after crystallisation from light petroleum (b. p. 40—60°), gave 4-methyl-3′-nitrodiphenyl, m. p. 75—77°, which gave a strong depression in m. p. on admixture with 2-methyl-3′-nitrodiphenyl (m. p. 72·5°) and showed no depression of m. p. on admixture with 4-methyl-3′-nitrodiphenyl which had been prepared from 4-acetamido-4′-methyldiphenyl as described in (*a*) above.

Structure of 2-methyl-3′-nitrodiphenyl. 2-Methyl-3′-nitrodiphenyl (5 g.) was reduced in the usual manner in ethanol solution with stannous chloride and hydrochloric acid. A portion (3·2 g.) of the resulting base (5·1 g.) was dissolved in 5N-sulphuric acid (20 ml.) and cooled to 0°, and the suspension of base sulphate diazotised with a solution of sodium nitrite (1·4 g.) in water (2 ml.). The diazonium solution was added to a cold solution of sodium hypophosphite (27 g.) in 5N-sulphuric acid (100 ml.), and the mixture was kept at 0° for two days. Extraction of the reaction mixture gave 2-methyldiphenyl which distilled as a colourless oil, b. p. 123°/13 mm. (1·1 g.), n_D^{20} 1·5933. Sherwood, Short, and Stansfield (*J.*, 1932, 1834) record b. p. 130—136°/27 mm. Oxidation of this hydrocarbon with boiling aqueous potassium permanganate afforded diphenyl-2-carboxylic acid, m. p. 112—113°, which showed no depression of m. p. on admixture with an authentic specimen, m. p. 113°. A second portion (2·0 g.) of the base was distilled at 94—100°/0·05 mm., and crystallisation from light petroleum (b. p. 40—60°) gave *3-amino-2′-methyldiphenyl* in colourless prisms, m. p. 37·5—38° (Found: C, 85·4; H, 7·1; N, 7·6. $C_{13}H_{13}N$ requires C, 85·2; H, 7·1; N, 7·6%). Passage of keten through a dry benzene solution of the base gave plates of *3-acetamido-2′-methyldiphenyl*, m. p. 94° (Found: C, 80·3; H, 6·8; N, 6·0. $C_{15}H_{15}ON$ requires C, 80·0; H, 6·7; N, 6·2%). Quantitative bromination of 3-amino-2′-methyldiphenyl hydrochloride (by the method described below) required three molecular proportions of bromine, thus confirming the *m*-position of the amino-group in the diphenyl molecule (Found: for 0·1 g. of base hydrochloride of 99·0% purity: 26·98 ml. of 0·1N-Br–BrO_3. Calc. for 3 mol. proportions: 27·34 ml.).

4-Methyl-2′-nitrodiphenyl. Diazotised *p*-toluidine was allowed to react with excess of nitrobenzene in the presence of aqueous potassium hydroxide as described by Grieve and Hey (*J.*, 1932, 1888). The resulting mixture of 4-methylnitrodiphenyls was allowed to crystallise, and the precipitated 4-methyl-4′-nitrodiphenyl was separated. The residual oil was twice fractionated through a 12-cm. Dufton column, and the middle cuts from the second fractionation (b. p. 179°/10 mm., n_D^{20} 1·6116) were bulked and induced to crystallise by strong cooling (solid carbon dioxide). 4-Methyl-2′-nitrodiphenyl crystallised from light petroleum (b. p. 40—60°) in pale yellow needles, m. p. 37—37·5°. The identity of the product as 4-methyl-2′-nitrodiphenyl was confirmed by reduction and acetylation to give the known 2-acetamido-4′-methyldiphenyl. The 4-methylnitrodiphenyl was reduced (stannous chloride) and acetylated by passing keten through the dry benzene solution of the base for 30 minutes. The resulting colourless solution was washed (aqueous sodium carbonate) and dried (K_2CO_3), and the benzene evaporated. The residual 2-acetamido-4′-methyldiphenyl crystallised from ether in colourless needles, m. p. 104° undepressed on admixture with an authentic specimen (m. p. 102—103°). Grieve and Hey (*loc. cit.*) record m. p. 103°.

2-, 3- and 4-Amino-4′-methyldiphenyl hydrochlorides. The three isomeric amino-4′-methyldiphenyl hydrochlorides were prepared as described above for the amino-4′-bromodiphenyl hydrochlorides.

Volumetric Determination of the Reference Compounds.—Each of the two series of three isomeric base hydrochlorides were estimated (*a*) as total base hydrochlorides by titration with alkali and (*b*) by nuclear bromination with a standard bromide–bromate mixture.

General procedure. (*a*) A known weight of the base hydrochloride (approx. 0·1 g.) was dissolved in a mixture of " AnalaR " acetone (25 ml.) and 0·1N-aqueous sodium hydroxide (20·00 ml.). In some estimations it was necessary to warm the mixture in order to facilitate dissolution. The excess of alkali was then back-titrated, when cold, with standard 0·1N-aqueous hydrochloric acid, methyl-red being used as indicator.

(*b*) Redistilled carbon tetrachloride (10 ml.) was added to a known weight of base hydrochloride (approx. 0·1 g.), followed by water (30 ml.) and excess of standard bromide–bromate solution (20·00 ml.; 0·2N. with respect to bromine). Finally, sulphuric acid (5 ml.; 10N.) was added and the flask

was quickly closed by a ground-in glass stopper and the mixture vigorously shaken for 30 minutes, all particles of base hydrochloride then having dissolved. The flask was then cooled to avoid loss of solution and bromine vapour by spurting on removal of the stopper due to pressure of carbon tetrachloride vapour inside the flask. Potassium iodide (15 ml.; 10% aqueous) was added, the mixture well shaken, and the iodine liberated by the excess of bromine titrated with standard thiosulphate (0·2N.). "AnalaR" potassium bromate which had been dried at 100° for 1 hour was used for preparation of the standard bromide–bromate solution ($KBrO_3$, 11·1340 g., and KBr, 140 g., in 2 l. of solution).

Results.—

Amino-4′-bromodiphenyl hydrochloride series

	Purity, %, by: acid–base titration	nuclear bromination
4-Amino-	99·7 ± 0·2	98·9 ± 0·4
3-Amino-	99·8 ,,	96·0 ,,
2-Amino-	98·3 ,,	98·4 ,,

Amino-4′-methyldiphenyl hydrochloride series

	Purity, %, by: acid–base titration	nuclear bromination
4-Amino-	98·8 ± 0·2	99·6 ± 0·4
3-Amino-	99·3 ,,	99·5 ,,
2-Amino-	98·5 ,,	98·7 ,,

Volumetric Determination of Mixtures of 2-, 3-, and 4-Nitrodiphenyl.—Reactions were carried out between nitrobenzene and (*a*) the sodium aryldiazoates (the Gomberg reaction), (*b*) the aryl diazoacetates (the labile tautomer of the acylarylnitrosamine), (*c*) the aroyl peroxides, and (*d*) the 1-aryl-3 : 3-dimethyltriazens in which the aryl group was successively *p*-bromophenyl and *p*-tolyl. The nitrobenzene used in these reactions was purified by shaking it with solid sodium hydroxide for 12 hours, followed by steam-distillation and drying (NaOH). The nitrobenzene was finally fractionated through a 70 × 3-cm. Fenske column and collected at 90—92°/14 mm. After completion of the reaction the dark nitrobenzene solution was heated with two successive portions of aqueous sodium hydroxide (20%), and after separation and washing with dilute acid the solution was finally dried (NaOH). After removal of excess of nitrobenzene by distillation through a 30-cm. Dufton column, the dark tarry residue was distilled and the resulting crude mixture of isomeric nitrodiphenyls was redistilled, care being taken to avoid contamination of the nitro-compounds with the last traces of nitrobenzene. The base hydrochlorides were prepared from the mixture of nitro-compounds after a normal stannous chloride reduction. Unless otherwise stated, the above procedure was used in all experiments, and the mixture of bases was not purified by distillation before preparation of the hydrochloride.

Control Determinations.—Numerous control determinations were carried out of which the following examples are typical. (*a*) Mixture of 4-bromo-4′- and -3′-nitrodiphenyls in excess of nitrobenzene. A mixture of 4-bromo-4′-nitrodiphenyl (91·34%) and 4-bromo-3′-nitrodiphenyl (8·66%) was heated to 150° with nitrobenzene (250 ml.) for 2 hours and then subjected to the procedure outlined above. The determination of base hydrochloride by acid–base titration showed 98·5% of amino-4′-bromodiphenyl hydrochloride. Nuclear bromination gave 6·7% of 3-amino-4′-bromodiphenyl hydrochloride.

(*b*) Mixture of 4-methyl-4′-, -3′-, and -2′-nitrodiphenyls in excess of nitrobenzene. A mixture of 4-methyl-4′- and -2′-nitrodiphenyl (88·95%) with 4-methyl-3′-nitrodiphenyl (11·05%) was dissolved in nitrobenzene (250 ml.), heated to 150° for 2 hours, and treated as described above. The determination of base hydrochloride by acid–base titration showed 99·2% of amino-4′-methyldiphenyl hydrochloride. Nuclear bromination gave 15·3% of 3-amino-4′-methyldiphenyl hydrochloride. A mixture of 4-methyl-4′- and -2′-nitrodiphenyl (93·5%) and 4-methyl-3′-nitrodiphenyl (6·5%), subjected to the same procedure as described above, gave base hydrochloride by acid–base titration 98·8%, and 8·8% of 3-amino-4′-methyldiphenyl hydrochloride by nuclear bromination.

Substitution Reactions of Nitrobenzene.

(a) *The Gomberg Reaction* (Gomberg and Bachmann, *J. Amer. Chem. Soc.*, 1924, **46**, 2339; Gomberg and Pernert, *ibid.*, 1926, **48**, 1372).—*The action of sodium* p-*bromobenzenediazoate on nitrobenzene.* (i) A solution of *p*-bromobenzenediazonium chloride was prepared in the usual manner by diazotisation of *p*-bromoaniline (43 g.) in concentrated hydrochloric acid (50 ml.) with 33% aqueous sodium nitrite (36 ml.). Chilled nitrobenzene (400 ml.) was added to the diazonium solution, followed by the slow addition of 5N-aqueous sodium hydroxide (150 ml.). When the addition had been completed, the nitrobenzene layer, which had become deep red, was separated and, on treatment as described above, gave a mixture of isomeric 4′-bromonitrodiphenyls, b. p. 130—175°/3 mm. (11 g., 16%). (ii) A second experiment, using the same procedure as described above, gave the isomeric 4′-bromonitrodiphenyls in 25% yield, b. p. 129—160°/0·5 mm.

The action of sodium p-*toluenediazoate on nitrobenzene.* (i) The diazonium solution, prepared in the normal manner from *p*-toluidine (21 g.) in concentrated hydrochloric acid (50 ml.) and sodium nitrite (20 g.) in water (30 ml.), was allowed to react with nitrobenzene (700 ml.) and worked up as described above. The isomeric 4′-methylnitrodiphenyls (19 g.) were obtained in 45% yield, with b. p. 97—108°/0·015 mm. (ii) In a second experiment the isomeric 4′-methylnitrodiphenyls were obtained, in 27% yield with b. p. 108—110°/0·015 mm., by the same procedure. In this instance the free base was isolated by distillation (b. p. 97—102°/0·02 mm.) before preparation of the hydrochloride. (iii) In a third reaction the isomeric 4′-methylnitrodiphenyls, b. p. 184—192°/9 mm., were obtained in 36% yield. The free base distilled at 175—180°/9 mm.

(b) *The Peroxide Reaction* (Hey and Walker, *J.*, 1948, 2213).—*The action of* p-*bromobenzoyl peroxide on nitrobenzene.* (i) *p*-Bromobenzoyl peroxide (Price, Kell, and Krebs, *J. Amer. Chem. Soc.*, 1942, **64**, 1104) (11·5 g.) was heated with nitrobenzene (140 ml.) at 150—160° for 4 hours. The resulting dark solution was worked up as described in section (a), but because there was a tendency for an emulsion to form when the nitrobenzene solution was being washed with dilute acid, chloroform (150 ml.) was added to aid the separation of the organic layer. The 4′-bromonitrodiphenyls (3·4 g.) were collected at 170—225°/0·2 mm. (ii) By the same procedure as above, 4′-bromonitrodiphenyls (5·0 g.), b. p. 154—170°/0·1 mm., were obtained from *p*-bromobenzoyl peroxide (12 g.).

The action of p-*toluoyl peroxide on nitrobenzene.* (i) *p*-Toluoyl peroxide, m. p. 133—134° (decomp.), was prepared by the procedure described for the preparation of aroyl peroxides by Hey and Walker (*loc. cit.*). Swain, Stockmayer, and Clark (*J. Amer. Chem. Soc.*, 1950, **72**, 5433) record m. p. 136—137° (decomp.). A solution of *p*-toluoyl peroxide (8 g.) in nitrobenzene (300 ml.) was heated at 150° for 4 hours and then left overnight before the dark solution was subjected to the usual working-up procedure. 4′-Methylnitrodiphenyls (5·4 g.), b. p. 106—110°/0·02 mm., were obtained. The free base (b. p. 94—100°/0·09 mm.) was isolated by distillation before preparation of the hydrochloride. (ii) By the same procedure as above, 4′-methylnitrodiphenyls (3·7 g.), b. p. 98—102°/0·05 mm., were obtained from *p*-toluoyl peroxide (6 g.). The base (b. p. 100—108°/0·1 mm.) was isolated by distillation before preparation of the hydrochloride.

(c) *The Acylarylnitrosamine Reaction.—The action of* p-*bromo-*N*-nitrosoacetanilide on nitrobenzene.* (i) The method of France, Heilbron, and Hey (*J.*, 1940, 369) was used for the preparation of the anilide, m. p. 87—88° (decomp.). Bamberger and Baudisch (*Ber.*, 1909, **42**, 3590) record m. p. 86—87° (decomp.). A solution of *p*-bromo-N-nitrosoacetanilide (5·9 g.) in nitrobenzene (250 ml.) was maintained at room temperature for 24 hours and was then heated at 150° for 2 hours before the product was subjected to the usual working-up procedure. The 4′-bromonitrodiphenyls (2·4 g.), b. p. 160—174°/1·0 mm., were obtained in 34% yield. (ii) By the procedure described above, a yield of 3·7 g. of 4′-bromonitrodiphenyls (44%) was obtained from the reaction of the nitroso-compound (7 g.) with nitrobenzene (250 ml.).

*The action of nitrosoaceto-*p-*toluidide on nitrobenzene.* (i) Nitrosoaceto-*p*-toluidide, m. p. 81·5° (decomp.), was prepared by the method described by France, Heilbron, and Hey (*loc. cit.*). Grieve and Hey (*J.*, 1935, 691) record m. p. 80° (decomp.). A solution of this toluidide (10 g.) in nitrobenzene (350 ml.) was maintained at 16° for 12 hours and then heated at 100° for 12 hours before the product was fractionally distilled without further treatment to yield, first, acetic acid, b. p. 20—30°/12 mm., and, secondly, nitrobenzene, b. p. 88°/12 mm. The residue was distilled to yield the 4′-methylnitrodiphenyls (3·8 g., 32%), b. p. 110—115°/0·04 mm. The corresponding base was isolated by distillation, b. p. 98—108°/0·015 mm., before preparation of the base hydrochloride. (ii) The 4′-methylnitrodiphenyls (1·7 g., 28%) were obtained by the decomposition of nitrosoaceto-*p*-toluidide (5 g.) in nitrobenzene (250 ml.), the product being subjected to the normal procedure. The free base, b. p. 91—100°/0·015 mm., was isolated by distillation before preparation of the hydrochloride.

(d) *The Triazen Reaction* (Elks and Hey, *J.*, 1943, 441).—*The action of* 1-p-*bromophenyl-*3 : 3-*dimethyltriazen on nitrobenzene.* (i) A solution of the triazen (17 g.) (specimen provided by Dr. J. M. Osbond) in nitrobenzene (200 ml.) was heated at 120° while dry hydrogen chloride was passed into the solution for 1 hour; the solution had then become deep red, and heating was discontinued. There was no precipitate of dimethylamine hydrochloride, even after the mixture had been kept overnight. The mixture was subjected to the usual procedure and the emulsion which had formed in the washing process was broken by the addition of an equal volume of chloroform. Distillation of the residue which remained after the solvents had been removed gave an orange-coloured liquid (11·2 g.), b. p. 130—164°/0·2 mm., which showed less tendency to crystallise than had previous products. (ii) A slow stream of hydrogen chloride was passed for 4 hours through a solution of 1-*p*-bromophenyl-3 : 3-dimethyltriazen (7·0 g.) in nitrobenzene (250 ml.) at 160°. The reaction product, an orange-coloured oil (4·6 g.), b. p. 116—148°/0·18 mm., was obtained from the nitrobenzene solution as in the previous reaction. Both products were shown on reduction and analysis of the base hydrochlorides to contain an impurity. A sample of the free base from reaction (ii) was regenerated from the hydrochloride with aqueous sodium hydroxide, extracted with ether, and dried over sodium hydroxide to ensure removal of traces of hydrogen chloride. The base, which distilled at 130—135°/0·13 mm., was found by sodium fusion to contain both bromine and chlorine. (iii) Prolonged passage of hydrogen chloride (9 hours) through a solution of 1-*p*-bromophenyl-3 : 3-dimethyltriazen (5 g.) in nitrobenzene (250 ml.) at 150°, followed by the normal working-up procedure, afforded a mixture of nitro-compounds (1·88 g.), b. p. 110—132°/0·05 mm. The corresponding mixture of free bases was isolated by distillation at 97—110°/0·015 mm. and found to contain both bromine and chlorine.

The anomalous results obtained by the volumetric determination of the samples of base hydrochlorides obtained from the three reaction products are due to a partial interchange of nuclear bromine and chlorine which takes place in the presence of the excess of hydrogen chloride necessary for the decomposition of the triazen.

The action of 3 : 3-*dimethyl-*1-p-*tolyltriazen on nitrobenzene.* (i) A current of dry hydrogen chloride was passed into a solution of 3 : 3-dimethyl-1-*p*-tolyltriazen (10 g.) (Hunter, *J.*, 1937, 324) in nitrobenzene (300 ml.) at 150° for 8 hours. The black reaction product was kept overnight before it was subjected to the usual working-up procedure. The isomeric 4′-methylnitrodiphenyls (7·1 g.), b. p. 104—110°/0·015 mm., were obtained in 54% yield. (ii) The isomeric 4′-methylnitrodiphenyls (3·3 g., 50%), b. p. 99—100°/0·012 mm., were obtained from the triazen (5 g.) by a method similar to that described above. The free base was isolated by distillation (b. p. 92—106°/0·07 mm.) before preparation of the hydrochloride.

The quantitative results obtained from the analysis of the products of the above reactions with nitrobenzene are summarised in the following table.

TABLE I.

Reaction of R·C_6H_4· *on nitrobenzene.*

	R = Br		R = Me	
Reaction	Acid–base titration : base hydrochloride, %	Nuclear bromination : 3-aminodiphenyl, %	Acid–base titration : base hydrochloride, %	Nuclear bromination : 3-aminodiphenyl, %
Sodium diazoate	99·2	12·5	—	—
	98·4	12·3	—	—
	—	—	98·3	9·4
	—	—	98·3	8·3
	—	—	98·7	9·1
Acyl peroxide	98·1	11·8	—	—
	99·5	11·6	—	—
	—	—	98·7	9·5
	—	—	98·1	9·2
Acylarylnitrosamine	98·8	11·9	—	—
	100·0	12·7	—	—
	—	—	100·0	8·7
	—	—	99·3	8·0
1-Aryl-3 : 3-dimethyltriazen	[104·5]	[21·7]	—	—
	[104·8]	[28·6]	—	—
	[109·7]	[24·5]	—	—
	—	—	96·7	7·0
	—	—	96·1	8·5
		Average 12·1%		Average 8·6%

The action of 3 : 3-*dimethyl*-1-o-*nitrophenyltriazen on benzene.* This *triazen*, prepared by the method of Elks and Hey (*loc. cit.*), crystallised from light petroleum (b. p. 40—60°) in slender yellow needles, m. p. 32° (Found : C, 49·45; H, 5·4. $C_8H_{10}O_2N_4$ requires C, 49·45; H, 5·15%). Hydrogen chloride was passed for 3 hours through a solution of the triazen (24 g.) in boiling benzene (200 ml.). The benzene solution was then washed with water and dried ($CaCl_2$). Evaporation of the benzene left a residue, which on distillation gave (*a*) a pale yellow liquid (5 g.), b. p. 110—135°/12 mm., and (*b*) a yellow liquid (6·4 g.), b. p. 135—170°/12 mm. Fraction (*a*) partly crystallised during 2 years at room temperature in a sealed tube, and further crystallisation from light petroleum (b. p. 40—60°) gave 2-chlorodiphenyl in colourless prisms, m. p. 31·5—32°, undepressed on admixture with an authentic specimen, m. p. 30—31°. Fraction (*b*) gave after redistillation *o*-chloronitrobenzene (1·5 g.), m. p. 31·5—32°, 2-chlorodiphenyl (2·4 g.), m. p. 31°, and 3 : 3-dimethyl-1-o-nitrophenyltriazen (1·7 g.), m. p. 30—32°. No 2-nitrodiphenyl was found in any of the fractions.

The action of 3 : 3-*dimethyl*-1-m-*nitrophenyltriazen on toluene.* The triazen, prepared by the general method of Elks and Hey (*loc. cit.*), was obtained in deep red tufts of prisms, m. p. 100°, which showed no depression of the m. p. on admixture with an authentic specimen (yellow needles, m. p. 99·5°). A second preparation afforded this triazen in yellow needles, m. p. 100°, with no trace of the red crystalline form. Both crystalline forms of this triazen showed remarkable stability towards hydrogen chloride in boiling toluene. Passage of hydrogen chloride through a boiling toluene solution of the triazen (red prisms) resulted in 50% recovery of the starting material in yellow needles. Prolonged passage of hydrogen chloride (24 hours) through a boiling toluene solution of the triazen afforded *m*-chloronitrobenzene (10%), unchanged triazen (20%), and a mixture of isomeric methyl-3′-nitrodiphenyls from which 2-methy-3′-nitrodiphenyl, m. p. 72·5—73°, was isolated (see above).

The Action of Benzoyl Peroxide on Nitrobenzene and the Isolation of 3-Nitrodiphenyl.—A solution of benzoyl peroxide (120 g.) in nitrobenzene (1·5 l.) was kept at 140° for 4 hours. Nitrobenzene (500 ml.) was distilled from the resulting dark solution and the residue was subjected to the normal working-up procedure. After distillation of the remaining nitrobenzene, the following six fractions were collected from the residue, which was distilled through a vacuum-jacketed column (50 cm., packed with metal gauze) kindly lent by Dr. G. H. Williams. Unless otherwise stated, the column was allowed to attain equilibrium for 5 minutes before samples of distillate were removed :

Fraction	Weight, g.	B. p.	Pressure, mm.	Remarks
i	18·0	150—161°	6	Yellow oil removed continuously
ii	17·2	158—163	7	
iii	3·0	162—166	5	Reflux ratio : 1 : 8
iv	2·6	165—169	5	Dark yellow oil
v	14·5	135—140	0·7	Residue from fractionation distilled without column
vi	3·1	170—200	0·1	

Fractions (i) and (ii) were crystallised (light petroleum, b. p. 40—60°), and the non-crystalline residues subjected to refractionation to yield 2-nitrodiphenyl (15 g.), m. p. 37·5°, 4-nitrodiphenyl (1·4 g.), m. p.

112—113°, and diphenyl (0·1 g.), m. p. and mixed m. p. 69° (cf. DeTar, *J. Amer. Chem. Soc.*, 1950, **72**, 1028). The remaining non-crystalline residues from fractions (i) and (ii) were reduced with stannous chloride and acetylated with acetic anhydride. Crystallisation from ethanol gave impure specimens of 2-acetamidodiphenyl, m. p. 116—117°, and 4-acetamidophenyl, m. p. 167—169°. Fractions (iii) and (iv) were crystallised (light petroleum, b. p. 40—60°) and gave 4-nitrodiphenyl (4·1 g.), m. p. 113°, and 2-nitrodiphenyl (0·7 g.), m. p. 36°. The non-crystalline residues, on reduction and acetylation, yielded mixtures of 2- and 4-acetamidophenyl only. Fraction (v) crystallised from ethanol in orange needles, m. p. 108—111° (impure 4-nitrodiphenyl; 12·4 g.). The residual oil from this crystallisation slowly deposited a semi-solid mass, which was separated and recrystallised first from ethanol and then from light petroleum (b. p. 40—60°), giving 3-nitrodiphenyl (0·25 g.) in buff plates, m. p. 57·5—58·5° undepressed on admixture with an authentic specimen, m. p. 58°. The identity of the 3-nitrodiphenyl thus obtained was further confirmed by reduction and acetylation to give 3-acetamidodiphenyl in white needles, m. p. and mixed m. p. 147·5°.

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KING'S COLLEGE, UNIVERSITY OF LONDON,
STRAND, LONDON, W.C.2.

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645. *The Hypophosphites of Tin.*

By DAVID A. EVEREST.

The following hypophosphites of bivalent tin have been prepared: $Sn(H_2PO_2)_2,6H_2O$; $Sn(H_2PO_2)_2$; $3Sn(H_2PO_2)_2,SnCl_2$; $Sn(H_2PO_2)_2,SnCl_2$. The existence of the quadrivalent tin hypophosphite, $Sn(H_2PO_2)_4,SnCl_4$, has been confirmed in the anhydrous state only. Conditions for the reduction of quadrivalent tin to the bivalent state by means of hypophosphorous acid have been established.

SINCE hypophosphorous acid has been used for reducing quadrivalent germanium to the bivalent state (Dennis and Hulse, *J. Amer. Chem. Soc.*, 1930, **52**, 3553), a reaction which can be quantitative under the correct conditions (Ivanov-Emin, *Zavod. Lab.*, 1947, **13**, 161), it was thought to be of interest to establish the conditions for a similar reduction of quadrivalent tin and to investigate the type and nature of the tin hypophosphites.

The only report hitherto on the tin hypophosphites was by Terni and Padovani (*Atti Accad. Lincei*, 1925, [vi], **2**, 501), who prepared $Sn(H_2PO_2)_4,SnCl_4,3H_2O$ by the action of sodium hypophosphite on a concentrated solution of stannic chloride. This substance was found to lose water when heated above 140°, and to decompose above 190° with evolution of phosphine. These authors did not observe any reduction of the quadrivalent tin by the sodium hypophosphite.

Of the corresponding lead compounds, the simple hypophosphite has been prepared as an anhydrous crystalline material by the action of sodium hypophosphite on a soluble lead salt (Rammelsburg, *J.*, 1873, **26**, 1; Rose, *Pogg. Ann.*, 1827, **9**, 225). This compound was only sparingly soluble in water. Two double lead hypophosphites have also been described, $Pb(H_2PO_2)_2,Pb(NO_3)_2$ (von Hertz, *Z. ges. Schiess. u. Sprengstoffw.*, 1916, **11**, 365; *Chem. Zentr.*, 1919, i, 271) and one with equimolecular parts of lead hypophosphite and lead styphnate (McNutt and Ehrlich, U.S.P. 2,352,964). Both these compounds were highly explosive. The information given about all three substances was scanty and of little assistance in predicting the nature of the corresponding tin compounds.

Hypophosphites of Bivalent Tin.—Three distinct compounds have been isolated, *viz.*, stannous hypophosphite, $Sn(H_2PO_2)_2$ (m. p. 105°), and two double salts, $3Sn(H_2PO_2)_2,SnCl_2$ (m. p. 130°) and $Sn(H_2PO_2)_2,SnCl_2$ (m. p. 181°). In addition the hydrated stannous hypophosphite, $Sn(H_2PO_2)_2,6H_2O$ (m. p. 65—67°), was identified, and evidence for a second hydrate, $Sn(H_2PO_2)_2,2H_2O$ (m. p. 70—90°), has been obtained. These compounds were all fairly stable in air; they were soluble in dilute sulphuric and in dilute and concentrated hydrochloric and hypophosphorous acids, their solubility being decreased and their ease of oxidation heightened with increased chlorine content. They were all hydrolysed by water with formation of stannous hydroxide, the ease of hydrolysis falling off with decreasing solubility.

Concentrated sulphuric and nitric acids readily attacked them, sulphuric acid first liberating hydrogen chloride and then causing decomposition with deposition of phosphorus and formation of phosphine; nitric acid caused oxidation even in the cold, with evolution of nitrous fumes. No conditions were found under which hypophosphorous acid could reduce stannous compounds to the metal.

Hypophosphites of Quadrivalent Tin.—The only compound actually isolated was anhydrous $Sn(H_2PO_2)_4,SnCl_4$; Terni and Padovani (*loc. cit.*) had reported a hydrate, but no evidence of any definite hydrates could be obtained. $Sn(H_2PO_2)_4,SnCl_4$ was insoluble in most solvents but was dissolved by hot hydrochloric acid, the ease of solution rising with increased acid concentration. It was also slowly dissolved by concentrated hypophosphorous acid, in which it was very soluble, giving a yellow solution which was apparently the same as that formed when stannic hydroxide was dissolved in the same solvent. Concentrated sulphuric or nitric acids readily attacked it, the reaction being similar to that with the stannous hypophosphites. With water, it was hydrolysed to stannic hydroxide. As stated by Terni and Padovani, $Sn(H_2PO_2)_4,SnCl_4$ differed from the stannous hypophosphites in having no melting point; the substance usually decomposed at about 195°, although this was subject to variation, some samples not decomposing till above 220°.

Attempts were made to prepare stannic hypophosphite by dissolving chloride-free stannic hydroxide in hypophosphorous acid. It was extremely soluble, giving a yellow solution, the colour deepening with increased tin concentration. No solid compounds could be separated, for on evaporation these solutions set to a glass. Addition of alcohol gave a precipitate consisting principally of stannic hydroxide, hydrolysis having occurred.

Reduction of Quadrivalent Tin to the Bivalent State.—This reduction, which was slow, was carried out in an inert atmosphere, as aerial oxidation was rapid especially in the presence of hydrochloric acid. It was established (see p. 2905) that in 3N-hydrochloric acid, in the presence of excess of hypophosphorous acid, stannic chloride and $Sn(H_2PO_2)_4,SnCl_4$ were completely reduced to the bivalent state. In more dilute hydrochloric acid reduction was incomplete, and in the absence of hydrochloric acid, or if sulphuric acid was substituted for it, no reduction was observed.

No reduction was found when either stannic hydroxide or $Sn(H_2PO_2)_4,SnCl_4$ was heated with hypophosphorous acid. The reason for this is not clear, but it may be due to complex formation stabilising the quadrivalent state, a postulate which is supported by the extreme solubility of stannic hydroxide and $Sn(H_2PO_2)_4,SnCl_4$ in hypophosphorous acid. In other solvents the chief factor limiting the extent and rate of reduction is the sparse solubility of $Sn(H_2PO_2)_4,SnCl_4$, which is always precipitated when hypophosphorous acid is added to a solution of stannic chloride. The amount of reduction and the solubility both increased with increased hydrochloric acid concentration, and in 3N-sulphuric acid, in which it is insoluble, no reduction occurred.

Experimental.

(All m. p.s are uncorrected.)

Analytical Procedures.—Tin. Method 1. After reduction to the bivalent state by being boiled with nickel foil and hydrochloric acid (1 : 1) for 45 minutes, the cooled solution was titrated in an inert atmosphere with 0·1N-iodine (standardised with metallic tin).

Method 2. Bivalent tin was directly determined by addition of the sample dissolved in 10N-hydrochloric acid to excess of 0·1N-iodine (standardised against potassium iodate through sodium thiosulphate) and immediate back-titration with 0·1N-sodium thiosulphate. The procedure could only be applied when the sample dissolved readily in hydrochloric acid.

Hypophosphorous acid. The sample was dissolved as far as possible in 3N-sulphuric acid and this solution, together with any undissolved material, was added to excess of 0·3N-potassium permanganate. Reaction then took place according to the equation $Sn(H_2PO_2)_2 + 2KMnO_4 + 3H_2SO_4 = Sn(OH)_4 + 2H_3PO_4 + K_2SO_4 + 2MnSO_4$. In the absence of chloride the solution was warmed to 40° for 2 hours, or in presence of chloride left for 24—48 hours at room temperature, to allow completion of the reaction. Excess of 0·3N-oxalic acid was then added, and afterwards back-titrated with 0·3N-potassium permanganate. This procedure gave the total reduction equivalent of the compound rather than its hypophosphite content.

Chlorine. The sample was boiled with sodium carbonate solution, and after separation of the crystalline stannous oxide formed, the hypophosphite was oxidised with alkaline hydrogen peroxide (15-vol.). The solution was then acidified with 3N-nitric acid, any tin remaining being precipitated as hydroxide. After removal of the latter, the chloride was precipitated as silver chloride. The chief difficulty encountered was the complete oxidation of the hypophosphite, and as a result the silver chloride was usually contaminated with a little metallic silver formed by reduction of the silver nitrate. This was removed as far as possible by washing the precipitate with warm diluted nitric acid (1 : 1), but it was usually found that the chloride values obtained were slightly higher than the theoretical.

Stannous hypophosphite. Stannous hydroxide (Bury and Partington, *J.*, 1922, **121**, 1998) was dissolved in hot 25% hypophosphorous acid. On cooling, stannous hypophosphite hexahydrate (m. p. 65—67°) crystallised, the solutions showing supercooling. The crystals were washed with a little water and rapidly dried between sheets of filter-paper [Found: Sn, by method 2, 33·6. $Sn(H_2PO_2)_2,6H_2O$ requires Sn, 33·3%]. This *hydrate* lost water on being kept in air or washed with alcohol; when heated to 45—50° in a vacuum, the salt was completely dehydrated, giving the *hypophosphite* as a powder, m. p. 105°, and decomposing a few degrees above this temperature [Found: Sn, by method 2, 47·8; by method 1, 47·6%; reduction equiv., 25·0. $Sn(H_2PO_2)_2$ requires Sn, 47·7%; reduction equiv., 24·9].

When left for 12 hours in a vacuum at room temperature, the hexahydrate gave a *dihydrate* as a powder of indefinite m. p. (70—90°) [Found: Sn, by method 2, 41·6. $Sn(H_2PO_2)_2,2H_2O$ requires Sn, 41·7%].

Double Salt, $3Sn(H_2PO_2)_2,SnCl_2$.—This *salt* (m. p. 130°) [Found: Sn, by method 1, 50·6; by method 2, 50·2; Cl, 7·8%; reduction equiv., 29·3. $3Sn(H_2PO_2)_2,SnCl_2$ requires Sn, 50·7; Cl, 7·6%; reduction equiv., 29·2] was formed when a small quantity of hydrochloric acid was added to a warm solution of stannous hypophosphite in 25% hypophosphorous acid. A deficiency of hydrochloric acid was used in order to avoid precipitation of the less soluble $Sn(H_2PO_2)_2,SnCl_2$.

Double Salt, $Sn(H_2PO_2)_2,SnCl_2$.—This *salt* was prepared by dissolving the colourless crystalline precipitate (10 g.), obtained by the action of hypophosphorous acid on a solution of stannous chloride in 3*N*-hydrochloric acid, in 50% hypophosphorous acid (10 ml.) containing 10*N*-hydrochloric acid (15 ml.), and warming the solution for 30 minutes with metallic tin. When the solution was cooled in an inert atmosphere, crystals separated (m. p. 181°). These were rapidly filtered off, washed with a little water and absolute alcohol, and dried in a vacuum at 50—60° [Found: Sn, by method 1, 53·8; Cl, 16·7%; reduction equiv., 37·5. $Sn(H_2PO_2)_2,SnCl_2$ requires Sn, 54·2; Cl, 16·2%; reduction equiv., 36·5]. The analytical discrepancies are probably due to oxidation.

Double Salt, $Sn(H_2PO_2)_4,SnCl_4$.—Stannic chloride pentahydrate (5 g.) was dissolved in warm water (20 ml.), and 50% hypophosphorous acid (5 ml.) added; a thick white precipitate was rapidly formed. This was filtered off, washed with water and absolute alcohol, and dried in a vacuum at 50—60° to give the anhydrous *compound* [Found: Sn, by method 1, 37·5; Cl, 22·4%; reduction equiv., 41·3. $Sn(H_2PO_2)_4,SnCl_4$ requires Sn, 37·1; Cl, 22·2%; reduction equiv., 40·0]. The conditions for the isolation of the trihydrate prepared by Terni and Padovani (*loc. cit.*) were not established. Some samples of $Sn(H_2PO_2)_4,SnCl_4$ slowly liquefied whilst being dried. This was due to incomplete washing out of hypophosphorous acid and, when heated, this small amount of free acid was sufficient to dissolve the whole sample. This demonstrated the high solubility of $Sn(H_2PO_2)_4,SnCl_4$ in hypophosphorous acid.

Reduction Experiments.—The table shows the results of a series of reduction experiments. An inert atmosphere was maintained throughout.

Reduction soln. (vols., in ml.). H_3PO_2 (50%).	Other reagents.	Reduction, % after 45 mins.' boiling.	Reduction soln. (vols., in ml.). H_3PO_2 (50%).	Other reagents.	Reduction, % after 45 mins.' boiling.
		Reduction of $SnCl_4,5H_2O$ (1 g.).			
5	H_2O, 25	<1 *	5	1·5*N*-HCl, 25	45 *
5	3*N*-H_2SO_4, 25	<1 *	5	3*N*-HCl, 25	~100
5	0·1*N*-HCl, 25	4 *	5	6*N*-HCl, 25	~100
5	0·7*N*-HCl, 25	7 *			
		Reduction of $Sn(H_2PO_2)_4,SnCl_4$ (1 g.).			
5	H_2O, 25	<1 *	—	3*N*-HCl, 30	40
20	H_2O, 10	<1	5	3*N*-HCl, 25	~100

* Solutions where complete dissolution was not attained.

Percentage reduction was estimated by titrating the stannous tin with iodine (standardised against potassium iodate through sodium thiosulphate).

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, June 4th,* 1951.]

646. *Experiments on the Synthesis of the Pyrethrins. Part VII.* Synthesis of* trans-*Pyrethrone,* trans-*Pyrethrolone, and a Pyrethrin-I.*

By L. Crombie, S. H. Harper, and D. Thompson.

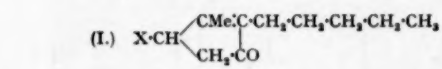
The structure of naturally derived pyrethrolone B-2 is established as (±)-4-hydroxy-3-methyl-2-*cis*(or *trans*)-*n*-penta-2′ : 4′-dienyl*cyclo*pent-2-en-1-one by oxidative and reductive degradation.

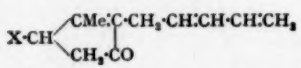
The use of *trans*-*n*-pent-2-en-4-yn-1-ol and of *trans*-*n*-penta-2 : 4-dien-1-ol as intermediates for eight- and seven-stage syntheses respectively of (±)-*trans*-pyrethrolone is studied. Semihydrogenation of *trans*-*n*-oct-5-en-7-yn-2-one is not stereospecific, and the resultant pyrethrone and pyrethrolone are impure. Pure products result from the use of *trans*-*n*-penta-2 : 4-dien-1-ol, prepared by the lithium aluminium hydride reduction of *trans*-*n*-penta-2 : 4-dienal. The structure of the resultant (±)-*trans*-pyrethrolone is confirmed by oxidative and reductive degradation. Comparison with naturally derived pyrethrolone B-2, in particular through their infra-red absorption spectra, shows lack of identity. By exclusion it is concluded that pyrethrolone B is *cis*-pyrethrolone.

Esterification of (±)-*trans*-pyrethrolone with (+)-*trans*-chrysanthemic acid provides the first total synthesis of a pyrethrin-I.

The structure of pyrethrolone, the major keto-alcoholic component of the pyrethrins (the potent insecticidal constituents of pyrethrum, *Chrysanthemum cinerariifolium*), has been the subject of controversy since its isolation by Staudinger and Ruzicka more than 35 years ago. As experimental evidence accumulated it became increasingly difficult to accommodate in one formula the conflicting requirements of ozonolyses, potassium permanganate oxidations, terminal methyl values, and ultra-violet light absorption data (for a review of this earlier work, see Harper, *Ann. Reports*, 1948, **45**, 162). Then, in 1944, LaForge and Barthel (*J. Org. Chem.*, 1944, **9**, 242; 1945, **10**, 106, 114) showed that pyrethrolone, as isolated from the pyrethrins, is heterogeneous and consists of the (+)- and (±)-forms of two isomeric pyrethrolones together with (+)- and (±)-cinerolone. Subsequent work by West (*J.*, 1946, 463) confirmed this but suggested that the (±)-forms of the keto-alcohols are artefacts and that only the (+)-forms are esterified with the chrysanthemumcarboxylic acids in the pyrethrins. Because of this heterogeneity of crude pyrethrolone much of the earlier evidence as to its structure is of dubious value. Nevertheless, that the pyrethrolones are hydroxy-3-methyl-2-*n*-pentadienyl-*cyclo*pent-2-en-1-ones had been established by the identity of tetrahydropyrethrone with dihydrojasmone (I; X = H) (LaForge and Haller, *J. Amer. Chem. Soc.*, 1936, **58**, 1777).

The structure of (±)-tetrahydropyrethrolone, obtained on hydrogenation of either of the (±)-pyrethrolones (" pyrethrolones B-2 and C-2," cf. LaForge and Barthel, *loc. cit.*, and West, *loc. cit.*), as (I; X = OH) was made probable by analogy with dihydrocinerolone and by synthesis of *n*-amylrethrolone (I; X = OH) (for an exposition of this nomenclature, see Harper, *Chem. and Ind.*, 1949, 636) through the action of *N*-bromosuccinimide on tetrahydropyrethrone and subsequent hydrolysis (Dauben and Wenkert, *J. Amer. Chem. Soc.*, 1947, **69**, 2074; Crombie, Elliott, and Harper, Part III, *J.*, 1950, 971). However, no direct comparisons of the synthetic and naturally derived keto-alcohols were made at that time.

(I.) 

 (II.)

Assignment of the side-chain double bonds of the pyrethrolones to the 2′ : 4′-positions as in (II) was made by LaForge and Barthel (*loc. cit.*) on the basis of quantitative hydrogenations of the semicarbazones and on the light absorption of the semicarbazones which showed a maximum at 2650 Å due to the C=C–C=N chromophore and in addition another maximum at 2280 Å due to the separate C=C–C=C of the side chain (cf. Gillam and West, *J.*, 1942, 671). Additional spectroscopic evidence for this assignment was subsequently provided by West (*loc. cit.*).

* Part VI, *J.*, 1951, 2445.

Such a structure for the pyrethrolones, containing one side-chain methyl group, is in agreement with the terminal methyl contents (1·0—1·1 groups) found by LaForge and Barthel (*loc. cit.*) but is at variance with those (1·2—1·5) found by West (*loc. cit.*). It conflicts, too, with the isolation by earlier workers of acetaldehyde with only small amounts of formaldehyde on ozonisation of pyrethrolone and it was largely on this fact that structures containing the ·CH_2·CH:C:CHMe side chain were proposed at various times (cf. Harper, *Ann. Reports*, 1948, **45**, 162). However, these discrepancies are now explicable on the assumption that cinerolone was present even in the " purified " pyrethrolone.

As a preliminary to attempting the synthesis of (±)-*cis*- and (±)-*trans*-pyrethrolone we have clarified some of the uncertainties regarding the structure of the pyrethrolones. We have synthesised *n*-amylrethrolone (I; X = OH) by another method (route *D*, cf. Part V, *J.*, 1950, 3552) which leaves no doubt as to its structure. Ethyl 2-keto-*n*-octane-1-carboxylate was hydrolysed and the sodium salt condensed with pyruvaldehyde in aqueous solution to give 3-hydroxy-*n*-undecane-2 : 5-dione. Cyclisation of this with aqueous alkali yielded *n*-amylrethrolone, from which the semicarbazone was obtained, though with difficulty. Hydrogenation of a specimen of pyrethrolone B-2 semicarbazone, kindly provided by Dr. F. B. LaForge, and direct comparison (by mixed melting point) of the product with the synthetic semicarbazone established the identity of tetrahydropyrethrolone with *n*-amylrethrolone and its structure as (I; X = OH). Ozonisation of pyrethrolone B-2, regenerated from the semicarbazone, and conversion of the volatile aldehydic product into the dimedon derivative, gave only the derivative of formaldehyde uncontaminated with that of acetaldehyde. As far as we are aware this is the first specimen of pyrethrolone that has not given appreciable or even preponderating amounts of acetaldehyde on ozonisation. This oxidative degradation provides the first clear chemical evidence for the presence of a terminal $=CH_2$ in the side chain of a pyrethrolone and in conjunction with the evident purity, the spectroscopic evidence, and the structure of tetrahydropyrethrolone establishes pyrethrolone B-2 as (±)-*cis*- or (±)-*trans*-*n*-penta-2 : 4-dienylrethrolone (II; X = OH). We have not been able to examine a specimen of pyrethrolone C-2 to establish whether it is a geometrical isomer of pyrethrolone B-2 or only an impure form of the latter. Hence our subsequent remarks are concerned only with pyrethrolone B-2.

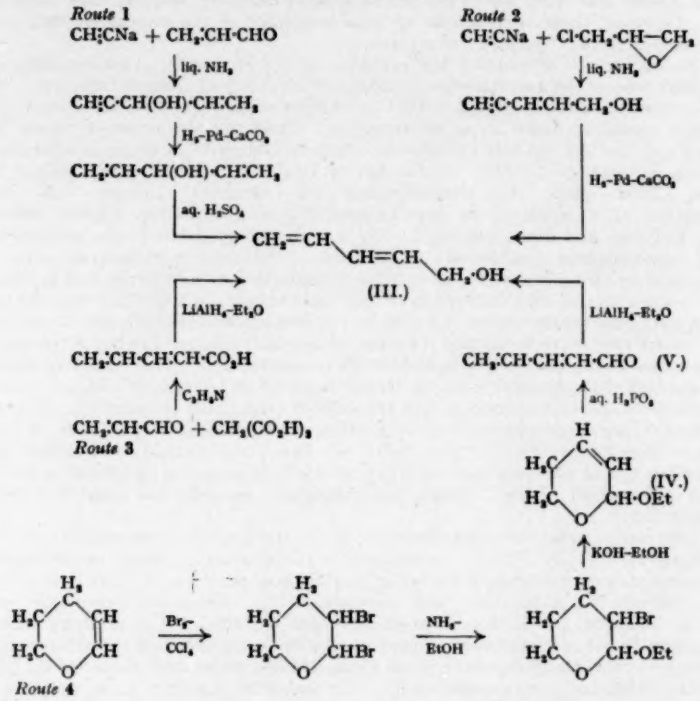
One of the most attractive intermediates for the synthesis of both pyrethrone (II; X = H) and pyrethrolone (II; X = OH) is *n*-penta-2 : 4-dien-1-ol (III), which would permit of a subsequent seven-stage synthesis of the latter by the use of our route *D* (Part V, *loc. cit.*). We therefore studied its preparation and stereochemistry. *n*-Penta-2 : 4-dien-1-ol was first described by Heilbron, Jones, McCombie, and Weedon (*J.*, 1945, 84) as resulting in low yield from the anionotropic rearrangement of penta-1 : 4-dien-3-ol (route 1 of the attached scheme). Its preparation in this manner and the ready formation of a maleic anhydride adduct (Heilbron *et al.*, *loc. cit.*) indicate a *trans*-configuration. It was later prepared in better yield by the semihydrogenation of *n*-pent-2-en-4-yn-1-ol (route 2; Heilbron, Jones, and Sondheimer, *J.*, 1947, 1586), the latter evidently having the *trans*-configuration. Confirmation of this is afforded by the formation of an *erythro*-triol from this *n*-pent-2-en-4-yn-1-ol by performic acid (Raphael, *J.*, 1949, S 44). In agreement with these conclusions we find that lithium aluminium hydride reduction of *n*-penta-2 : 4-dienoic acid (almost certainly having the *trans*-configuration because of its preparation by the Knoevenagel reaction; see Lauer and Gensler, *J. Amer. Chem. Soc.*, 1945, **67**, 1171) gives the same alcohol (route 3).

We find that *trans*-*n*-penta-2 : 4-dien-1-ol is also formed in good yield by lithium aluminium hydride reduction of the *n*-penta-2 : 4-dienal obtained on ring fission of 2-ethoxydihydropyran (route 4) (Woods and Sanders, *J. Amer. Chem. Soc.*, 1946, **68**, 2483), despite the fact that the internal ethylenic bond is initially constrained into the *cis*-configuration. Inversion appears to occur at the ring-fission stage, for the *n*-penta-2 : 4-dienal itself gives a maleic anhydride adduct (*idem*, *ibid.*, 1947, **69**, 2926). Except for citral *a* and *b*, which are not strictly analogous as they do not contain the R·CH:CH·CHO structure, we have been unable to find any well-established example of a *cis*-αβ-ethylenic aldehyde of this type. Semihydrogenation of αβ-acetylenic acetals followed by acid hydrolysis gives *trans*-αβ-ethylenic aldehydes (Lohaus, *J. pr. Chem.*, 1928, [ii], **119**, 235; Sondheimer, private communication), whereas semihydrogenation of αβ-acetylenic aldehydes themselves gives either *trans*- or impure products (Lohaus, *loc. cit.*; Bourgeul, *Bull. Soc. chim.*, 1929, [iv], **45**, 1067). It would appear that *cis*-αβ-ethylenic aldehydes are particularly unstable (in the presence of acid?) and difficult to isolate.

The identity of these four preparations of *trans*-*n*-penta-2 : 4-dien-1-ol was established by

the mixed melting points of their 1-naphthylurethanes and of their maleic anhydride adducts. Furthermore they had the same infra-red spectra in the range 8—11 μ. in which differences due to geometrical isomerism should have been evident. The *trans-n*-penta-2 : 4-dien-1-ol obtained

Routes to trans-n-*penta*-2 : 4-*dien*-1-*ol*.



by route 4 boiled sharply, had a constant refractive index (n_D^{20} 1·4896), and was free from monoethylenic and saturated contaminants. In contrast Heilbron, Jones, and Sondheimer (*loc. cit.*) recorded a boiling point and refractive index spread (n_D^{18} 1·4770—1·4893), which we have confirmed, for *trans-n*-penta-2 : 4-dien-1-ol made by the semihydrogenation of *trans-n*-pent-2-en-4-yn-1-ol (route 2) over palladium–calcium carbonate. It is evident the semihydrogenation of this enyne system is not entirely selective under these conditions as will be further exemplified below.

We have also made a preliminary examination of the semihydrogenation of *n*-pent-4-en-2-yn-1-ol as a route to *cis-n*-penta-2 : 4-dien-1-ol. With Isler's palladium–charcoal catalyst (deactivated by quinoline) (Isler, Huber, Ronco, and Kofler, *Helv. Chim. Acta*, 1947, **30**, 1911) hydrogenation was not fully selective and although hydrogenation was stopped when only 0·9 mol. of hydrogen had been absorbed some monoethenoid or saturated product was present. This process and others for the introduction of the *cis-n*-penta-2 : 4-dienyl system are being further investigated.

As the enyne system of *trans-n*-pent-2-en-4-yn-1-ol is more stable than the diene system of *trans-n*-penta-2 : 4-dien-1-ol, the latter alcohol polymerising to a gel in the course of a few days at room temperature, our initial approach to (±)-*trans*-pyrethrolone (detailed in the chart below) started from the acetylenic alcohol with the intention of postponing semihydrogenation to as late a stage as possible. Treatment of *trans-n*-pent-2-en-4-yn-1-ol with phosphorus tribromide and pyridine gave impure bromide, but phosphorus trichloride and pyridine gave the pure chloride (VI) in good yield. Alkylation of ethyl sodioacetoacetate with this chloride

followed by ketonic fission gave *trans*-*n*-oct-5-en-7-yn-2-one (VII), whose structure was confirmed by its light absorption (see Table I) and by quantitative hydrogenation to *n*-octan-2-one, identified as its 2 : 4-dinitrophenylhydrazone.

TABLE I.

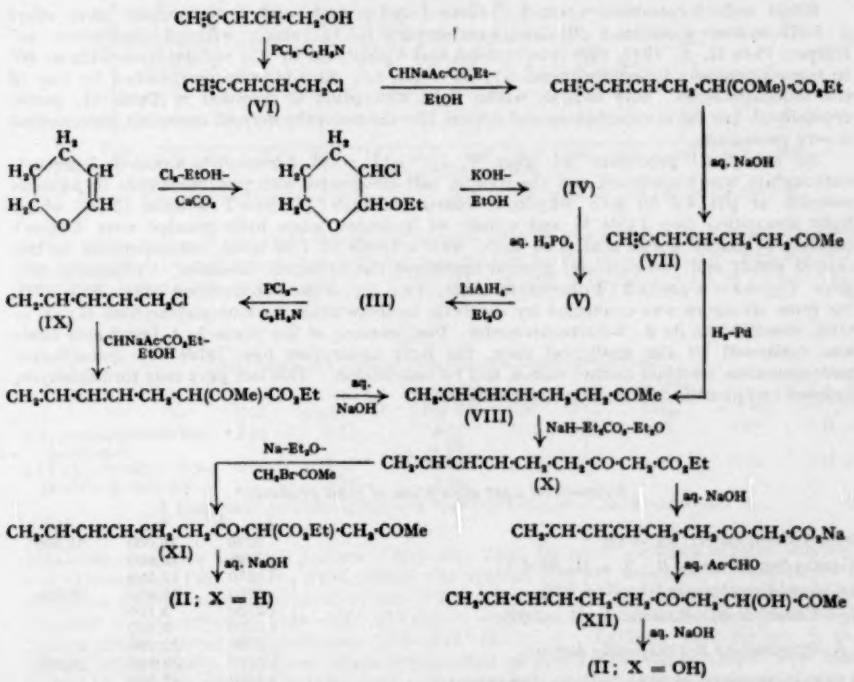
Ultra-violet light absorption of intermediates.

	$\lambda_{max.}$, Å.	$\varepsilon_{max.}$
$CH{\equiv}C{\cdot}CH{:}CH{\cdot}CH_2{\cdot}OH$(*trans*)	2230	15,000 *
	(Infl. 2290	10,000) *
$CH_2{:}CH{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}OH$	2270	11,900
$CH_2{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}OH$(*trans*) (III)	2260	25,200
$CH{\equiv}C{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}COMe$(*trans*) (VII)	2230	14,000
$CH_2{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}COMe$(*trans*) (VIII)	2260	23,000
†	2230	21,500
$CH_2{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et$(*trans*) (X)	2260	27,800
†	2240	23,000
$CH_2{:}CH{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH(OH){\cdot}COMe$(*trans*) (XII)	2260	27,500

* Data of Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583.

† The best specimens of dienes obtained from (VII) by the semihydrogenation route; the other dienes were obtained without semihydrogenation from (III) prepared by route 4.

As the next step, carbethoxylation, required the formation of the sodio-derivative of the ketone, semihydrogenation was carried out at this point to avoid the complication due to the ethynyl hydrogen atom. The use of either palladium–calcium carbonate or authentic Isler's



catalyst for the semihydrogenation of the ketone (VII) did not produce exclusively the diene : fractional distillation gave the pure diene (VIII) though in much reduced yield. *trans*-*n*-Octa-5 : 7-dien-2-one (VIII) was characterised by its light absorption (see Table I), a 2 : 4-dinitrophenylhydrazone, and a maleic anhydride adduct.

To avoid the necessity for semihydrogenation attention was turned to the use of *trans-n*-penta-2 : 4-dien-1-ol (III), prepared by route 4. We found, in Woods and Sander's procedure (*loc. cit.*), the isolation of 2 : 3-dibromotetrahydropyran and its subsequent reaction with alcoholic ammonia rather unsatisfactory, uncontrollable decomposition of the dibromide being frequent (cf. Paul, *Bull. Soc. chim.*, 1934, [v], **1**, 1397). The use of 2 : 3-dichlorotetrahydropyran, prepared in ether (cf. Crombie and Harper, *J.*, 1950, 1707), was more satisfactory, as was a procedure based on B.P. 598,080 (Jones, Bremner, and Imperial Chemical Industries Limited, 1948), for without isolation from ethanolic solution the 3-chloro-2-ethoxytetrahydropyran could be treated with potassium hydroxide to give the ethoxydihydropyran (IV). Interaction of *trans-n*-penta-2 : 4-dien-1-ol with phosphorus trichloride in pyridine at −10° gave *trans-n*-penta-2 : 4-dienyl chloride (IX) in good yield. We had considered at the outset of these experiments the direct preparation of the corresponding bromide by allylic bromination of *trans*-piperylene. However, we could not induce reaction between *N*-bromosuccinimide and *trans*-piperylene at atmospheric pressure, even in the presence of benzoyl peroxide or of another reacting olefin. Alkylation of ethyl sodioacetoacetate with the chloride (IX) followed by ketonic fission gave *trans-n*-octa-5 : 7-dien-2-one (VIII), identical with the ketone prepared by semihydrogenation apart from the slightly more intense light absorption (see Table I).

Carbethoxylation of (VIII) by ethyl carbonate was best effected in presence of sodium hydride, and although hydrogen is liberated reduction of the diene system of the resultant ethyl 2-keto-*trans-n*-octa-5 : 7-diene-1-carboxylate (X) was negligible as shown by the light absorption of the product (see Table I). Presumably an important factor is the low potential at which hydrogen is liberated from sodium hydride (Hansley and Carlisle, *Chem. Eng. News*, 1945, **23**, 1332).

Ethyl sodio-2-keto-*trans-n*-octa-5 : 7-diene-1-carboxylate and bromoacetone gave ethyl 2 : 5-diketo-*trans-n*-undeca-8 : 10-diene-4-carboxylate (XI), which without distillation (cf. Harper, Part II, *J.*, 1946, 892) was cyclised and hydrolysed by 3% sodium hydroxide at 40° to *trans-n*-penta-2 : 4-dienylrethrone (II; X = H), *i.e.*, *trans*-pyrethrone (purified by way of the semicarbazone). One sample, whose light absorption is recorded in Table II, partly crystallised, but the semicarbazone and ketone, like the naturally derived materials, deteriorated slowly on storage.

By our usual procedure (cf. Part V, *loc. cit.*) ethyl 2-keto-*trans-n*-octa-5 : 7-diene-1-carboxylate was hydrolysed and the sodium salt condensed with pyruvaldehyde in aqueous solution at pH 8·5 to give 3-hydroxy-*trans-n*-undeca-8 : 10-diene-2 : 5-dione (XII), whose light absorption (see Table I) and uptake of hydrogen when hydrogenated over Adams's catalyst in glacial acetic acid (4·04 mols. with a break at 1·96 mols., corresponding to two double bonds and two carbonyl groups) confirmed the expected structure. Cyclisation then gave (±)-*trans-n*-penta-2 : 4-dienylrethrolone, *i.e.*, (±)-*trans*-pyrethrolone (II; X = OH). Its gross structure was confirmed by catalytic hydrogenation to *n*-amylrethrolone (I; X = OH), identified as its 3 : 5-dinitrobenzoate. The presence of the penta-2 : 4-dienyl side chain was confirmed by the analytical data, the light absorption (see Table II), quantitative hydrogenation, terminal methyl values, and by ozonisation. This last gave only formaldehyde, isolated and identified as its dimedon derivative.

TABLE II.

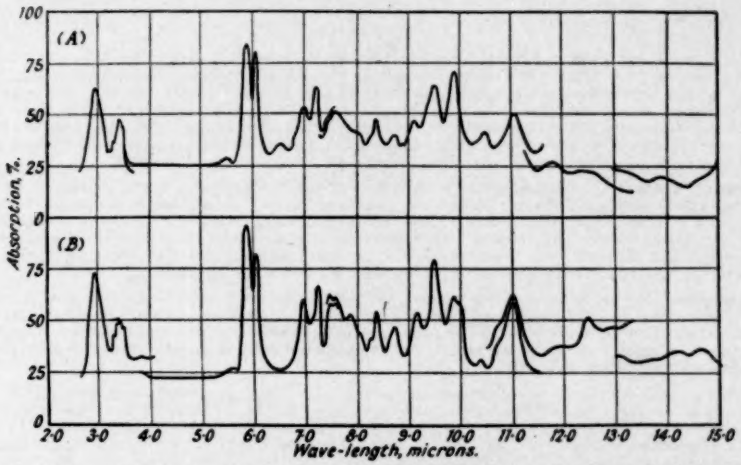
*Ultra-violet light absorption of final products.**

	$\lambda_{max.}$, Å	$\varepsilon_{max.}$	$\Delta\varepsilon$ †
trans-Pyrethrone (II; X = H)	2270	34,000	21,500
Tetrahydropyrethrone (I; X = H) (Part V)	2340	13,800	—
	2270	12,500	—
(±)-*trans*-Pyrethrolone (II; X = OH)	2270	33,000	23,900
(±)-Tetrahydropyrethrolone (I; X = OH)	2220	9,100	—
	2270	9,100	—
(±)-Pyrethrolone B-2 (naturally derived)	2230	29,900	—
	2270	29,900	20,800
(±)-*trans*-Pyrethronyl (+)-*trans*-chrysanthemate	2220	47,500	—
	2270	47,500	19,500
(±)-*trans*-Tetrahydropyrethronyl (±)-*trans*-chrysanthemate (Part III)	2230	28,000	—
	2270	28,000	—

* All determined with a Hilger Medium Quartz Spectrograph.
† Increase of ε at 2270 Å (*ca.* $\lambda_{max.}$) due to the $CH_2{:}CH{\cdot}CH{:}CH$ chromophore.

It must be mentioned that contamination by quite small amounts of saturated or monoethylenic impurites in the intermediates becomes magnified in subsequent stages. This is due to the instability of the diene components which are preferentially destroyed, thus concentrating the impurities, as is shown by the falling off of the $\varepsilon_{max.}$ due to the diene chromophore. A pure diene starting material is thus essential. At each subsequent stage the product was fractionally distilled and the presence of the intact diene system confirmed by ultra-violet light absorption measurement and by quantitative microhydrogenation.

Finally it remains to consider the relation of this synthetic (±)-*trans*-pyrethrolone to the naturally derived racemic pyrethrolones. Restricting attention to pyrethrolone B-2, for the



A. (±)-trans-*Pyrethrolone* (*synthetic*). *B.* (±)-*Pyrethrolone B-2* (*naturally derived*).

reason given above, it is evident that any difference must be due to a differing configuration of the side chain. Inspection of their infra-red spectra (see figure) shows that although the main structural features are very similar [see Table III; cf. the infra-red spectra of (±)-*cis*- and

TABLE III.

*Chief infra-red light absorption structural correlations.**

	Bonded OH.	Unsatd. aliph. C–H.	Satd. C–H, CH_2, CH_3.	C=O.	C=C.	Satd. CH_2, CH_3.	C–CH_3.	*sec.* OH.
(±)-*trans*-Pyrethrolone (synthetic)	2·94	3·31	3·42 3·50	5·89	6·05	6·99	7·22	9·52 μ
(±)-Pyrethrolone B-2 (naturally derived)	2·93	3·31 (3·36)	3·42 3·50	5·89	6·05	6·98	7·23	9·50 μ

* Discussion of other features is reserved for a later communication.

(±)-*trans*-cinerolone (Cupples, *J. Amer. Chem. Soc.*, 1950, **72**, 4522; Crombie, Harper, Stedman, and Thompson, Part VI, *J.*, 1951, 2445)] the spectra are not identical. Non-identity of (±)-*trans*-pyrethrolone with pyrethrolone B-2 is supported by the melting point of *trans*-pyrethrone semicarbazone [198—200° (decomp.)] which is some 18° below that recorded for the naturally derived semicarbazone [216—218° (decomp.); LaForge and Haller, *J. Org. Chem.*, 1938, **2**, 546]. However, these preparations of pyrethrone semicarbazone were made before the heterogeneity of pyrethrolone was recognised, so that this evidence must not be weighted unduly. Rather similar evidence is the inability to prepare a solid semicarbazone from (±)-*trans*-pyrethrolone, but it must be borne in mind that the naturally derived semicarbazones have always been prepared indirectly from the pyrethrin or pyrethronyl acetate semicarbazones. By exclusion, therefore, pyrethrolone B-2 is (±)-*cis*-pyrethrolone; a

conclusion which is supported by the analogy of the *cis*-configuration of naturally derived cinerolone and by the repeated failures to obtain a diene adduct from pyrethrolone or its derivatives (LaForge and Haller, *loc. cit.*; West, *J.*, 1944, 239; cf. Robey, *Science*, 1942, **96**, 470).

From synthetic (±)-*trans*-pyrethrolone the first total synthesis of a pyrethrin-I has now been accomplished by esterification with (+)-*trans*-chrysanthemic acid [for identity of the synthetic and natural (+)-acid see Campbell and Harper, *J.*, 1945, 283]. The acid chloride and *trans*-pyrethrolone in pyridine gave a synthetic pyrethrin-I consisting of the diastereoisomeric pair of esters, (±)-*trans*-pyrethronyl (+)-*trans*-chrysanthemate, whose light absorption is recorded in Table II.

Experimental.

M. p.s are uncorrected and were determined in capillary tubes unless otherwise stated. Microanalyses are by Drs. Weiler and Strauss, Oxford, and by Mr. Oliver, Imperial College. Microhydrogenations were carried out in acetic acid over Adams's catalyst, by Mr. Oliver. The ultra-violet light-absorption data were determined in purified ethanol by Drs. Weiler and Strauss, and by Mrs. Boston, Imperial College, with a Hilger Medium Quartz Spectrograph. Infra-red light absorption data were determined by one of us (L. C.) with a Grubb Parsons single-beam spectrometer coupled to a Brown recorder, the pure liquids being used as capillary films of *ca.* 5-μ. thickness.

Naturally Derived Pyrethrolone B-2.—A mixture of pyrethrolone B-2 semicarbazone (500 mg.), m. p. 204—206° (decomp.), oxalic acid (1·0 g.), and water (5 ml.) was heated on the steam-bath with passage of a stream of nitrogen. After 30 minutes the solid had disappeared and the liberated keto-alcohol was taken up in ether, washed with aqueous sodium hydrogen carbonate, dried, and distilled. Pyrethrolone B-2 (200 mg.) was collected as a single pale fraction, n_D^{20} 1·5406 (light absorption: see Table II); uptake on microhydrogenation, 3·80 mols., 3|= and 1 carbonyl group.

Ozonisation. Excess of ozone was passed through a carbon tetrachloride solution (5 ml.) of pyrethrolone B-2 (146 mg.) at 20° and then through aqueous dimedon. Water was then added and nitrogen bubbled for 20 hours through the whole. The dimedon derivative was crystallised once from 50% aqueous ethanol, to give the formaldehyde derivative (46 mg.), m. p. 188°, raised to 188—189° on admixture with authentic material.

Hydrogenation. Pyrethrolone B-2 semicarbazone (43 mg.) in ethyl acetate (5 ml.) was hydrogenated over 5% palladium–calcium carbonate (*ca.* 30 mg.). As reduction was slow further catalyst was added (uptake of hydrogen: *ca.* 2 mols.). The catalyst was removed ("Filtercel") and the filtrate concentrated to small bulk, (±)-tetrahydropyrethrolone semicarbazone separating as clusters of short needles, m. p. 176·5—177·5° with softening from 172·5°. On a Kofler hot stage this had m. p. 172—174°, whereas a mixture with the synthetic semicarbazone described below had m. p. 170—171°.

(±)-*Tetrahydropyrethrolone.*—By procedure *A* of Part V ethyl 2-keto-*n*-octane-1-carboxylate (23 g., the preparation described in *J.*, 1950, 3552) was shaken with 3% aqueous sodium hydroxide (180 ml.) for 6 hours and then the solution of the sodium salt condensed with aqueous pyruvaldehyde (26 ml.) during 6 hours at 35° and then overnight at room temperature. Isolation as described and distillation at 0·2 mm. gave several fractions, of which those having b. p. 104—124° and n_D^{20} 1·4542—1·4582 (5·24 g.) represented a 23% yield of 3-*hydroxy*-n-*undecane*-2 : 5-*dione* (Found: C, 67·1; H, 10·1. $C_{11}H_{20}O_3$ requires C, 66·1; H, 10·1%).

By the procedure described in Part V, 3-hydroxy-*n*-undecane-2 : 5-dione (5·24 g.) was cyclised in 3% aqueous sodium hydroxide (90 ml.) at room temperature. Fractional distillation gave (±)-tetrahydropyrethrolone (1·9 g., 40%), b. p. 120—128°/0·1 mm., n_D^{20} 1·4856 (light absorption, see Table II; uptake on microhydrogenation, 2·13 mols., 1|= and 1 carbonyl group). The 3 : 5-dinitrobenzoate had m. p. 98—99° (Kofler hot stage), when crystallised from methanol, not depressed when admixed with the derivative of the same m. p. from the reduction of (±)-*trans*-pyrethrolone, described below. The semicarbazone had m. p. 167—169° (Kofler hot stage).

trans-n-*Oct*-5-*en*-7-*yn*-2-*one.*—*trans*-*n*-Pent-2-en-4-yn-1-ol (Haynes, Heilbron, Jones, and Sondheimer, *J.*, 1947, 1583) is vesicant, and admission of air on to the hot tarry still residue causes an explosion (this tar is soluble in hot pyridine), and its sodium derivative is pyrophoric. It darkens on storage, but a sample kept for 18 months in a refrigerator and then redistilled gave pure material without significant loss.

Phosphorus trichloride (142 g.) was added dropwise to a mixture of *trans*-*n*-pent-2-en-4-yn-1-ol (230 g.) and pyridine (56 ml.) at −10°, the mixture becoming green and finally blue. The mixture was then kept for 12 hours under nitrogen and the product (242 g.) distilled at 72—82°/150 mm. On redistillation *trans*-*n*-pent-2-en-4-ynyl chloride (215 g., 76%) had b. p. 80°/175 mm., n_D^{20} 1·4932 (Found: C, 58·7; H, 4·9; Cl, 36·7. Calc. for C_9H_4Cl: C, 59·7; H, 5·0; Cl, 35·3%). Heilbron, Jones, Lacey, McCombie, and Raphael (*J.*, 1945, 77) recorded b. p. 82—84°/200 mm., n_D^{20} 1·4842 for this chloride prepared by another method.

The above procedure gave *trans*-*n*-pent-2-en-4-ynyl bromide (46% yield) as a turbid unstable product, b. p. 92—100°/16 mm., n_D^{20} 1·538.

trans-*n*-Pent-2-en-4-ynyl chloride (215 g.) was added dropwise with stirring during 2 hours to a refluxing solution of ethyl sodioacetoacetate [from ethyl acetoacetate (286 g.), sodium (50·6 g.), and

ethanol (1·5 l.)]. After refluxing for a further 30 minutes the ethanol was distilled off through a short column under reduced pressure. The residual crude ethyl α-pentenynylacetoacetate was stirred at room temperature with 5% aqueous sodium hydroxide (2 l.) during 4 hours, then a little undissolved oil removed, and the brown aqueous layer acidified with 50% sulphuric acid (200 ml.). When this was heated to 50° in a flask fitted for steam-distillation decarboxylation started and the ketone thus produced was isolated by steam-distillation, about 2 l. of distillate being collected. This was saturated with salt and extracted twice with ether. Fractional distillation of the dried (Na_2SO_4) extract then gave trans-n-*oct-5-en*-7-*yn*-2-*one* (76·8 g., 32%), b. p. 86—88°/10 mm., n_D^{20} 1·4788, having an odour reminiscent of that of *n*-octan-2-one (Found: C, 77·35, 77·2; H, 8·1, 8·35. $C_8H_{10}O$ requires C, 78·65; H, 8·25%); for light absorption, see Table I. The 2 : 4-*dinitrophenylhydrazone* crystallised in flattened buff-orange needles (from ethanol), m. p. 124° (Found: C, 55·6; H, 5·0; N, 17·9. $C_{14}H_{14}O_4N_4$ requires C, 55·6; H, 5·0; N, 18·5%).

When hydrogenated in ethanol (7 ml.) over 5% palladium–barium sulphate, *trans-n*-oct-5-en 7-yn-2-one (104 mg.) absorbed 59 ml. of hydrogen at N.T.P. (Calc. for 2|=: 61 ml.). After removal of the catalyst ("Filtercel"), 2 : 4-dinitrophenylhydrazine (170 mg.) and a drop of hydrochloric acid were added to the filtrate and the mixture refluxed briefly. Concentration and crystallisation gave *n*-octan-2-one 2 : 4-dinitrophenylhydrazone (210 mg.), m. p. 58°, not depressed on admixture with an authentic specimen of m. p. 59°.

Semihydrogenation of trans-n-*Oct-5-en*-7-*yn*-2-*one*.—*trans-n*-Oct-5-en-7-yn-2-one (56·4 g.) was shaken in hydrogen over Isler's deactivated palladium–charcoal catalyst (0·8 g.) in ethyl acetate (60 ml.). When 10·15 l. of hydrogen had been absorbed (Calc. for the conversion of an acetylenic to an ethylenic bond: 10·3 l.) hydrogenation was stopped, "Filtercel" added, and the catalyst filtered off. Ethyl acetate was distilled from the filtrate through a column and the residue fractionally distilled at 22 mm., to give the following fractions: (i) b. p. 81—84·0°, n_D^{20} 1·4471 (1·76 g.); (ii) b. p. 84·0—85·0°, n_D^{20} 1·4601 (3·69 g.); (iii) b. p. 85·0—86·0°, n_D^{20} 1·4633 (9·55 g.); light absorption, $\lambda_{max.}$ 2240 Å, $\varepsilon_{max.}$ 13,000; (iv) b. p. 86·0—86·5°, n_D^{20} 1·4663 (9·16 g.); (v) b. p. 86·5—87·0°, n_D^{20} 1·4693 (8·80 g.); light absorption, $\lambda_{max.}$ 2220 Å, $\varepsilon_{max.}$ 20,000; (vi) b. p. 87·0—87·5°, n_D^{20} 1·4712 (7·90 g.); (vii) b. p. 87·5—88·0°, n_D^{20} 1·4724 (5·98 g.); light absorption, $\lambda_{max.}$ 2230 Å, $\varepsilon_{max.}$ 19,500; (viii) b. p. 88·0—89·0°, n_D^{20} 1·4717 (1·11 g.); (ix) b. p. 89—96°, n_D^{20} 1·4797 (2·50 g.). Fractions (v)—(vii) represent a 40% yield of trans-n-*octa*-5 : 7-*dien*-2-*one* (Found: C, 77·45; H, 9·75. $C_8H_{10}O$ requires C, 77·45; H, 9·65%). The above is typical of several semihydrogenations carried out with Isler's catalyst; a similar result was obtained with palladium–calcium carbonate. The light absorption quoted in Table I for *trans-n*-octa-5 : 7-dien-2-one is that of the best material isolated.

The 2 : 4-*dinitrophenylhydrazone* crystallised in long orange needles, m. p. 79°, from ethanol (Found: C, 54·9; H, 5·3; N, 18·4. $C_{14}H_{16}O_4N_4$ requires C, 55·2; H, 5·3; N, 18·2%). A warm mixture of *trans-n*-octa-5 : 7-dien-2-one (124 mg.) and maleic anhydride (98 mg.) in benzene (1 ml.) was set aside until the adduct separated as transparent rectangular plates which became opaque on exposure to air. 3-3'-*Keto*-n-*butyl*cyclo*hex*-4-*ene*-1 : 2-*dicarboxylic anhydride* on crystallisation from benzene had m. p. 90—91° (Found, on material dried at 60° *in vacuo*: C, 65·0; H, 6·05. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%).

trans-n-*Penta*-2 : 4-*dien*-1-*ol*.—(a) *Route* 3. To freshly recrystallised vinylacrylic acid (10 g.; *Ber.*, 1937, **70**, 2388) covered with ether (50 ml.) and cooled in ice, lithium aluminium hydride (2·85 g.) in ether (200 ml.) was added slowly with stirring. The reaction mixture was cautiously treated with water, then just acidified, and the ethereal layer separated (a ball of polymerised acid remained, consequently the reduction of the unpolymerised acid was carried out with a large excess of reductant). Distillation of the dried ethereal solutions gave *trans-n*-penta-2 : 4-dien-1-ol (1·5 g.), b. p. 66—68°/26 mm., n_D^{20} 1·4838 (this indicates the presence of a trace of more saturated material) (Found: C, 71·1; H, 9·8. Calc. for C_5H_8O: C, 71·5; H, 9·6%). The 1-naphthylurethane initially had m. p. 87°, but recrystallisation from light petroleum (b. p. 60—80°) gave superb needles, of m. p. 99·0—99·5° alone or mixed with a specimen (m. p. 97—98°) obtained by Heilbron, Jones, McCombie, and Weedon (*J.*, 1945, 84) (route 1) or with a specimen obtained by route 2, or with the further sample described below. The adduct formed from maleic anhydride (0·25 g.) and *trans-n*-penta-2 : 4-dien-1-ol (0·20 g.) in warm benzene was converted into the γ-lactone of 3-hydroxymethyl*cyclo*hex-4-ene-1 : 2-dicarboxylic acid on crystallisation from water and this formed needles, m. p. 177°, not depressed on admixture with a specimen of the same m. p. obtained by Heilbron *et al.* (*loc. cit.*), or with the preparation described below.

(b) *Route* 4. Woods and Sanders's procedure (*J. Amer. Chem. Soc.*, 1946, **68**, 2483) was modified as follows: Dihydropyran (504 g.), diluted with carbon tetrachloride (300 ml.), was kept at −35° to −45° (solid carbon dioxide–alcohol) during the slow addition of bromine (960 g.). After removal from the cooling bath excess of bromine was decolorised by a few drops of dihydropyran. The solvent was removed under reduced pressure on a *warm* water-bath, and the crude yellow (though on several occasions partial decomposition occurred during this process with consequent darkening in colour) 2 : 3-dibromotetrahydropyran added to cooled (0°) anhydrous ethanol (2·5 l.) saturated with ammonia. After 12 hours at room temperature ammonium bromide was filtered off and to the boiling filtrate potassium hydroxide pellets (600 g.) were added in portions. The mixture was refluxed for 6 hours and then as much ethanol as possible was removed by distillation. The residue, diluted with water, was extracted several times with ether, and the extracts were dried (Na_2SO_4) and distilled, to give 2-ethoxy-5 : 6-dihydro-2-pyran (315—330 g., 41—43%), b. p. 153—163°, mainly b. p. 154—158°, n_D^{20} 1·442—1·445. Towards the end of the distillation, if overheating occurs, a violent reaction sets in and penta-2 : 4-dienal distils; presumably acid is liberated, inducing fission of any ethoxydihydropyran remaining undistilled. Appreciable loss occurs on redistillation.

Chlorine was passed into dihydropyran (252 g.), diluted with dry ether (500 ml.), at 0°, until a green

colour persisted. The solution was decolorised by a few drops of dihydropyran, and the solvent removed by distillation under reduced pressure. The crude 2 : 3-dichlorotetrahydropyran was added to ethanolic ammonia and the preparation completed as described above, to give 2-ethoxy-5 : 6-dihydro-2-pyran (199 g., 52%), b. p. 50—60°/12 mm., n_D^{20} 1·441—1·444.

In another experiment chlorine was passed into a mixture of dihydropyran (152 g.), ethanol (1 l.), and precipitated calcium carbonate (360 g.), cooled below 10°, until 42 l. had been absorbed. The reaction mixture was heated to boiling, potassium hydroxide (140 g.) added, and the preparation completed as above, to give 2-ethoxy-5 : 6-dihydro-2-pyran (89 g., 38%), b. p. 154—157°, n_D^{20} 1·443.

By Woods and Sanders's procedure (*loc. cit.*) 2-ethoxy-5 : 6-dihydro-2-pyran (400 g.) was converted into *trans-n*-penta-2 : 4-dienal (63 g., 25%), b. p. 38—40°/20 mm., n_D^{20} 1·514. These authors recorded a 55% yield on a 40-g. scale, which we have never achieved on the larger scale, of pentadienal having n_D^{25} 1·5163. Pentadienal was stored at 0° in the presence of quinol.

To a solution of *trans-n*-penta-2 : 4-dienal (64·5 g.) in dry ether (400 ml.), cooled in ice, an assayed ethereal solution of lithium aluminium hydride (7·48 g. in 177 ml.) was added slowly with stirring. Water was then added cautiously, followed by dilute sulphuric acid, and the product isolated from the dried (Na_2SO_4) ethereal layer by distillation. *trans-n*-Penta-2 : 4-dien-1-ol (47·4 g., 77%) had b. p. 75—76°/32 mm., 55—57°/12 mm., n_D^{20} 1·4890 (Found: C, 71·3; H, 9·7. Calc. for C_5H_8O: C, 71·5; H, 9·6%); light absorption, see Table I. A similar yield of pentadienol, having n_D^{20} 1·4890, was obtained on addition of the ethereal pentadienal to a stirred suspension of lithium aluminium hydride in ether. The pentadienol was stored at 0° in the presence of quinol. The 1-naphthylurethane on crystallisation from light petroleum had m. p. 89°, but on seeding with the derivative described above this m. p. at once rose to 99·5°. The lactonic acid adduct from maleic anhydride had m. p. 177°.

trans-n-Penta-2 : 4-dien-1-ol (410 mg.), reduced in ethyl acetate over palladium–barium sulphate, absorbed 218 ml. of hydrogen at N.T.P. (Calc. for 2|=: 219 ml.). However, microhydrogenation gave an uptake of 2·25 mols., which is attributed to partial hydrogenolysis of the allylic hydroxyl group.

trans-n-*Penta*-2 : 4-*dienyl Chloride*.—Phosphorus trichloride (25 g.) was added slowly to a stirred mixture of *trans-n*-penta-2 : 4-dien-1-ol (42 g.) and pyridine (10 ml.) at −10° and then the crude chloride was distilled from the reaction mixture under reduced pressure. This product was washed successively with water, aqueous sodium hydrogen carbonate, and hydrochloric acid, dried ($CaCl_2$), and distilled to give trans-n-*penta*-2 : 4-*dienyl chloride* (46 g., 92%), b. p. 80—82°/240 mm., n_D^{20} 1·492—1·493 (Found: Cl, 34·1. C_5H_7Cl requires Cl, 34·6%).

trans-n-*Octa*-5 : 7-*dien*-2-*one*.—By a procedure similar to that used for the preparation of *trans-n*-oct-5-en-7-yn-2-one, *trans-n*-penta-2 : 4-dienyl chloride (46 g.) was caused to react with ethyl sodioacetoacetate [from sodium (9·9 g.) and ethyl acetoacetate (56 g.) in ethanol (300 ml.)] and subsequently treated with 5% aqueous sodium hydroxide (800 ml.). Isolation of the product as described above and distillation gave *trans-n*-octa-5 : 7-dien-2-one (26 g., 47%), b. p. 75—78°/12 mm., n_D^{20} 1·4768 (1·474—1·477); light absorption, see Table I; uptake on microhydrogenation, 3·20 mols. with a break at 2·01 mols. (2|= and 1 carbonyl group) (Found: C, 77·5; H, 9·95. Calc. for $C_8H_{12}O$: C, 77·45; H, 9·95%). The 2 : 4-dinitrophenylhydrazone had m. p. 82·0—82·5° (Found: C, 55·65; H, 5·55. Calc. for $C_{14}H_{16}O_4N_4$: C, 55·2; H, 5·3%), not depressed on admixture with the somewhat lower-melting derivative obtained from the semihydrogenation of *trans-n*-oct-5-en-7-yn-2-one and described above. *trans-n*-Octa-5 : 7-dien-2-one was stored at 0° in the presence of quinol.

Ethyl 2-*Keto*-trans-n-*octa*-5 : 7-*diene*-1-*carboxylate*.—*trans-n*-Octa-5 : 7-diene-2-one (26 g.) was added dropwise to a stirred refluxing suspension of sodium hydride (10·1 g.) in ethyl carbonate (47 ml.) and ether (60 ml.) during 2 hours. Next day *ethyl* 2-*keto*-trans-n-*octa*-5 : 7-*diene*-1-*carboxylate* (17·3 g., 42%), was isolated by the procedure of Part V; it had b. p. 82—90°/0·1 mm., n_D^{20} 1·477—1·482 (Found: C, 67·5, 66·9; H, 8·35, 8·35. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%); light absorption, see Table I; uptake on microhydrogenation, 2·70 mols. with a break at 2·01 mols. (2|= and 1 carbonyl group). Similar experiments with octa-5 : 7-dien-2-one, prepared by semihydrogenation, yielded products having, *e.g.*, b. p. 75·5—78·0°/0·08 mm., n_D^{20} 1·476—1·479; light absorption, $\lambda_{max.}$ 2250 Å, $\varepsilon_{max.}$ 18,600; (Found: C, 66·4, 66·0, 66·55, 66·35; H, 8·25, 8·65, 8·65, 8·55. $C_{11}H_{16}O_3$ requires C, 66·3; H, 9·05%).

trans-*Pyrethrone*.—Ethyl 2-keto-*trans-n*-octa-5 : 7-diene-1-carboxylate (3·5 g.) was added to a suspension of powdered sodium (0·54 g.) in ether, and the mixture set aside to complete the formation of the sodio-derivative. Next day freshly distilled bromoacetone (4·0 g.) was added and the mixture refluxed for 2 hours. Aqueous acid was then added, the ethereal layer separated and evaporated, and the residual oil stirred in 3% aqueous sodium hydroxide (90 ml.) at 40° during 3 hours. Acidification, extraction, and distillation gave crude *trans*-pyrethrone (0·65 g.), b. p. 92—115°/0·25 mm., n_D^{20} 1·514—1·516. This ketone was converted, in pyridine–ethanol, into the *semicarbazone*, which after crystallisation from aqueous ethanol had m. p. 198—200° (Found: C, 65·45; H, 7·75. $C_{12}H_{17}ON_3$ requires C, 65·8; H, 7·75%); light absorption, $\lambda_{max.}$ 2260 (ε 25,100) and 2645 Å (ε 22,400); side-chain methyl groups, 1·16, 1·27.

A suspension of the semicarbazone (400 mg.) in water (0·6 ml.) and oxalic acid (600 mg.) was heated under reflux in nitrogen for 1 hour. Cooling, extraction with light petroleum (b. p. 40—60°), and distillation gave trans-*pyrethrone*, b. p. 70—72°/0·08 mm., n_D^{20} 1·5350 (Found: C, 78·2; H, 8·6. $C_{11}H_{14}O$ requires C, 81·45; H, 8·7%) (the tendency for these ketones to give low values for carbon was noted in Part II, *J.*, 1946, 892); light absorption, see Table II; uptake on microhydrogenation, 3·5 mols. with a break at 2·82 mols. (3|= and 1 carbonyl group). This particular specimen of *trans*-pyrethrone partly crystallised and the solid had m. p. *ca.* 60°.

Similar experiments with ethyl 2-keto-*n*-octa-5 : 7-diene-1-carboxylate, prepared by the semihydrogenation route, yielded a pyrethrone having, *e.g.*, b. p. 85—90°/0·25 mm., n_D^{20} 1·4996, which on

conversion into the semicarbazone (sodium acetate–aqueous ethanol) and crystallisation from methanol gave a product, m. p. 199—200° (decomp.) with softening from 192°; light absorption, $\lambda_{max.}$ 2270 (ε 18,600) and 2640 Å (ε 26,300). The less pure products obtained by the semihydrogenation route all had $\varepsilon_{max.}$ at *ca.* 2260 Å less than $\varepsilon_{max.}$ at *ca.* 2645 Å.

3-*Hydroxy*-trans-n-*undeca*-8 : 10-*diene*-2 : 5-*dione*.—By procedure *A* of Part V, ethyl 2-keto-*trans*-*n*-octa-5 : 7-diene-1-carboxylate (18 g.) was hydrolysed in 3% aqueous sodium hydroxide (140 ml.) during 6 hours at 20° and the solution of sodium salt then condensed with aqueous pyruvaldehyde (21·2 ml.) during 6 hours at 35° and then 5 hours at 20°. The fractions of the product, isolated as described, boiling within the range 102—128°/0·15 mm., and having n_D^{20} 1·498—1·504 (6·05 g.), represented a 33% yield of 3-*hydroxy*-trans-n-*undeca*-8 : 10-*diene*-2 : 5-*dione* (Found: C, 67·7; H, 8·2. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%); light absorption, see Table I; uptake on microhydrogenation, 4·04 mols. with a break at 1·96 mols. (2|═ and 2 carbonyl groups).

(±)-trans-*Pyrethrolone*.—By the procedure of Part V 3-hydroxy-*trans*-*n*-undeca-8 : 10-diene-2 : 5-dione (6·1 g.) was cyclised in 6% aqueous sodium hydroxide (90 ml.) during 2 hours and the product isolated as described. Two distillations gave (±)-trans-*pyrethrolone* (1·45 g., 26%), b. p. 120—122°/*ca.* 0·1 mm., n_D^{20} 1·540—1·546 (Found: C, 73·75; H, 8·0. $C_{11}H_{14}O_3$ requires C, 74·1; H, 7·9%); light absorption, see Table II; uptake on microhydrogenation, 4·10, 3·87 mols. with a break at 3·08 mols. (3|═ and 1 carbonyl group); side-chain methyl groups, 1·14. Attempts to prepare the semicarbazone and the acetate semicarbazone were fruitless.

Ozonisation of (±)-trans-*Pyrethrolone*.—By the method used for pyrethrolone B-2 (see above), (±)-*trans*-pyrethrolone (150 mg.) gave formaldehyde dimedon derivative (32 mg.), m. p. 188—189° not depressed on admixture with authentic formaldehyde derivative.

Hydrogenation of (±)-trans-*Pyrethrolone*.—(±)-*trans*-Pyrethrolone (100 mg.) in ethyl acetate (15 ml.) was reduced over 5% palladium–barium sulphate (100 mg.) (uptake: *ca.* 2 mols.). Distillation of the catalyst-free solution then gave (±)-tetrahydropyrethrolone (63 mg.), b. p. 115—116°/0·1 mm., n_D^{20} 1·4902. The 3 : 5-dinitrobenzoate had m. p. 99° (Kofler hot stage), when crystallised from methanol, not depressed when admixed with the derivative described above.

(±)-trans-*Pyrethronyl* (+)-trans-*Chrysanthemate*.—By the procedure of Part V, interaction of (±)-*trans*-pyrethrolone (450 mg.) and (+)-*trans*-chrysanthemoyl chloride (470 mg.) in benzene (10 ml.)–pyridine (0·4 ml.) gave (±)-trans-*pyrethronyl* (+)-trans-*chrysanthemate* (300 mg.), b. p. 112—113°/2 × 10^{-3} mm., n_D^{20} 1·5210 (Found: C, 76·0; H, 8·3. $C_{21}H_{28}O_5$ requires C, 76·8; H, 8·6%); light absorption, see Table II; uptake on microhydrogenation, 5·95 mols. (4|═, 1 carbonyl group, and hydrogenolysis of one ester group) [for comparison, (±)-tetrahydropyrethronyl (±)-*trans*-chrysanthemate (Part III) gave an uptake of 3·22 mols. with a break at 2·84 mols. (2|═, 1 carbonyl group, and hydrogenolysis of one ester group), while a specimen of allethrin gave an uptake of 4·30 mols. (3|═, 1 carbonyl group, and hydrogenolysis of one ester group)].

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Imperial College of Science and Technology,
South Kensington, London, S.W.7. (L. C.)

King's College (University of London),
Strand, W.C.2. (S. H. H., D. T.)

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647. *The Dehydration of Gypsum. Part III.* A Study of the Process of Dehydration and Rehydration of Gypsum by Adsorption Methods.*

By S. J. Gregg and E. G. J. Willing.

Samples of gypsum have been dehydrated at a succession of temperatures between 110° and 700°, and the surface area of the product has been estimated by carbon tetrachloride adsorption, both before and after the determination on it of the adsorption isotherm of water vapour at 25°. The surface area is, in general, diminished by the water treatment. In two cases a series of isotherms of carbon tetrachloride and of water vapour were alternately measured, and it was found that treatment by water did not diminish the uptake of *water* in a second run.

Taken together, the results suggest that the maxima at *ca.* 180—190° and at *ca.* 300° in the curve of surface area against temperature, referred to in Part I (Fig. 2), originate in the reactions: gypsum ⟶ hemihydrate + water and hemihydrate ⟶ anhydrite + water respectively.

As shown in Part II,* the adsorption of carbon tetrachloride can be used to measure the relative (and perhaps absolute) surface area of the dehydration product of gypsum obtained at different temperatures. In the present paper, an experimental study is described in which this adsorption is used to throw light on the chemical and physical changes which occur when gypsum is dehydrated and rehydrated.

Experimental.

Materials.—The gypsum was part of the batch described in Part I; the carbon tetrachloride was purified as described in Part II. The water was ordinary distilled water and had been freed from air by distillation *in vacuo* whilst in the storage section of the apparatus.

Procedure.—The apparatus was that described in Part II, with the addition of a storage system for water and a mercury cut-off for the controlled admission of the water vapour to the sorption balance.

3—4 g. of the dehydrated gypsum (prepared on the thermal balance as described in Part I) were weighed into the platinum bucket of the sorption balance, and an asbestos plug was inserted above the solid to prevent loss by spurting. The outer limb of the balance was placed in position, and the joint waxed over in the manner described in Part II; the sample was then outgassed at a definite temperature (usually between 80° and 90°) till no further loss in weight was registered on the recording drum. The connection to the pump was then closed, and the heating oven replaced by a water-bath kept at 25° ± 0·05°. Admission of vapour began after an hour or so had been allowed for thermal equilibration.

A number of isotherms were determined consecutively on each sample. The general plan was to use carbon tetrachloride adsorption and to follow the change in area produced by water adsorption and desorption on a sample prepared at a given temperature of preparation. The experiments fell into two main groups: in Group *A*, which included most of the samples, three isotherms only were determined on a given sample, *viz.*, carbon tetrachloride followed by water vapour, then again by carbon tetrachloride. In Group *B* a more detailed study with certain individual and typical samples was made, the general idea again being to use carbon tetrachloride isotherms to measure the effect of controlled water treatment, on the area of the sample.

Results.—The carbon tetrachloride isotherms have the general characteristics already described in Part II; equilibration was rapid, the carbon tetrachloride could be completely pumped off at 25°, and all the indications pointed to purely physical adsorption.

With water vapour the isotherm shows quite different characteristics. The curve rises steeply at first, running almost parallel to the adsorption axis, the corresponding pressure being almost too small to be measured accurately (cf. *AB* in Fig. 1). After this initial portion *AB*, the curve bends round sharply, becoming concave to the pressure axis, and gives relatively small increases in adsorption over the pressure range *ca.* $0{\cdot}1 < p/p_0 < 0{\cdot}8$; it finally becomes steep again as p/p_0 approaches unity. Except at the higher pressures (where several hours were required) equilibrium was reached within 30 minutes and usually within 5—10 minutes; at pressures above $p/p_0 = 0{\cdot}8$ it was difficult to reproduce points exactly, presumably owing to slow equilibration. The desorption branch shows peculiar features: usually the isotherm is nearly flat at first, it then falls very steeply, and finally there is another nearly flat portion, the whole giving a stepwise appearance. A second sharp fall occurs at low pressures. Equilibrium at all points on the desorption curve was reached in *ca.* 20 minutes.

* Part II, *J.*, 1951, 2378.

A portion of the water could not be removed by pumping at 25° even for 12 hours. The amount thus retained (point *D*, Fig. 1) varied from one sample to another according to the temperature of preparation, and always exceeded the uptake at point *B* on the adsorption branch. This " retained " water could be entirely removed by pumping for a few minutes with the sample heated to 85°.

The experiments of Group *A* will be described first. On each sample there was determined first a carbon tetrachloride isotherm [CCl_4(i)]; the sample was then outgassed at 25°, whereupon the carbon tetrachloride was completely and quickly removed; a water isotherm was then determined [H_2O(i)], and the water was removed by outgassing first at 25° and then at 85°; and finally a second carbon tetrachloride isotherm was determined [CCl_4(ii)]. The water isotherms are shown in Fig. 2; typical carbon tetrachloride isotherms have been given in Part II.

FIG. 1.

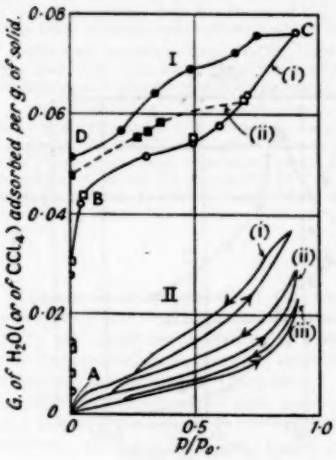

FIG. 2.

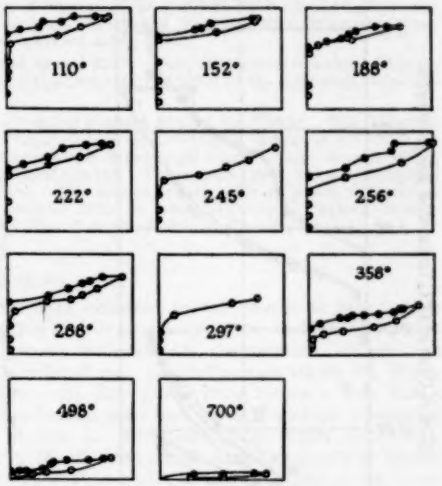

FIG. 1.

Adsorption isotherms of water vapour at 25° and of carbon tetrachloride at 25° on gypsum dehydrated at 288° (Expt. B, 1) : I, H_2O; II, CCl_4.

The isotherms were determined in the order : CCl_4(i); H_2O(i); CCl_4(ii); H_2O(ii); CCl_4(iii).

○, H_2O(i) *adsorption;* ●, H_2O(i) *desorption.* □, H_2O(ii) *adsorption;* ■, H_2O(ii) *desorption.*

FIG. 2.

Adsorption isotherms at 25° of water vapour on gypsum dehydrated at a series of temperatures (T). *The value of* T° *is marked on each graph.*

Ordinates : Adsorption, in g. per g. Abscissæ : Relative pressure.

The length of the vertical sides of each rectangle corresponds to 0·01 *g. of water vapour per g. of dehydrated gypsum, and the length of the horizontal sides to a relative pressure of* 1·0 (p/p_0) (p = *equilibrium pressure,* p_0 = *saturated vapour pressure, of water vapour*).

○ *Adsorption.* ● *Desorption.*

On all samples (except those prepared at 500° and upwards) the second carbon tetrachloride isotherm lay below the first, showing that the water treatment had in some way reduced the surface area, *S*. The ratio of the two areas, S_I/S_{II}, was taken as equal to the ratio of the amount of carbon tetrachloride adsorbed on the first and on the second isotherm respectively, at a relative pressure of 0·5. On plotting this ratio against the temperature of preparation, the curve of Fig. 4 was obtained. Typical water isotherms are plotted on a larger scale in Figs. 1 and 3 (Curves I), along with the corresponding carbon tetrachloride isotherms (Curves II).

The second group of experiments, *B*, was now carried out to try to throw some light on the cause of this decrease in area brought about by water treatment.

Experiment B, 1. The sample was prepared by heating gypsum for 75 minutes at 288°. The following isotherms were determined in succession: CCl_4(i)–outgas at 25°–H_2O(i)–outgas at 25°, then 85°–CCl_4(ii)–outgas at 25°–H_2O(ii)–outgas at 25°–CCl_4(iii)–outgas at 25° then 85°. The results are given in Fig. 1. The first three runs correspond to those of Group *A*; and CCl_4(ii) lies, as expected, below CCl_4(i). The second water isotherm [H_2O(ii)] was carried up to a water content only slightly

exceeding that retained at point *D* of the first run [H_2O(i)]. The solid was now outgassed at 25° so that the retained water was not removed, and a carbon tetrachloride isotherm [CCl_4(iii)] was immediately determined. As will be seen, this last isotherm runs below both CCl_4(i) and CCl_4(ii), showing that the water treatment has still further reduced the surface area. The " retained " water was removable, in the usual way, by pumping at 85°.

Experiment B, 2. The sample was prepared by heating gypsum for 2 hours at 256°. The following isotherms were determined: CCl_4(i)–outgas at 25°–H_2O(ia), to point *F*–outgas at 25°–CCl_4(ii)–outgas at 25°–H_2O(*ib*) from *F* onwards–outgas at 25°–CCl_4(iii)–outgas at 25° then 85°–CCl_4(iv)–outgas at 25°–H_2O(ii).

FIG. 3.

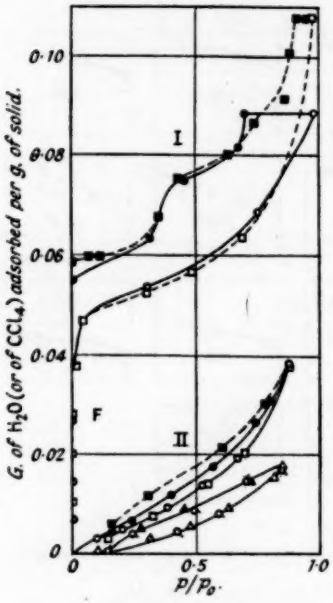

FIG. 4.

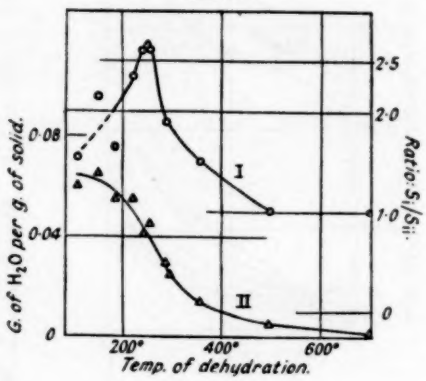

FIG. 3.

Adsorption isotherms of water vapour at 25° and of carbon tetrachloride at 25° on gypsum dehydrated at 256° (Expt. B, 2).

The isotherms were determined in the order: CCl_4(i); H_2O(ia) *to point* F; CCl_4(ii); H_2O(ib) *from* F *onwards*; CCl_4(iii); CCl_4(iv); H_2O(ii).

○, ● H_2O(i); □, ■ H_2O(ii); ○, ● CCl_4(i); □, ■ CCl_4(ii); ○, ○′, ●, ●′ CCl_4(iii); △, ▲ CCl_4(iv).

FIG. 4.

Curves for properties of gypsum dehydrated at a series of temperatures.

I. *The ratio* S_I/S_{II} (S_I = *surface area before,* S_{II} = *surface area after, exposure to water vapour*). *Use right-hand ordinates.*

II. *The amount,* x_{AB}, *of water adsorbed up to a point corresponding to point* B *of Fig.* 1. *Use left-hand ordinates.*

The results are given in Fig. 3. The first carbon tetrachloride isotherm [CCl_4(i)] was of the usual type In the first water isotherm the measurements were taken up only to point *F* on the initial steep portion *AB*; on outgassing at 25°, *no* water was lost, strongly suggesting that it is held by chemisorption or by chemical combination. Continuing from *F*, the carbon tetrachloride isotherm [CCl_4(ii)] obtained had an adsorption branch which coincided within experimental limits with that of CCl_4(i). [The *desorption* branch differed from CCl_4(i) for a reason which is not apparent.] It seems then that the water present has no effect on the magnitude or the nature of the surface area of the solid; this means that the water cannot be adsorbed on the surface of the solid, for the carbon tetrachloride would then

either have to compete with it for room, or else would be adsorbed on top of the water layer; in either of these cases the carbon tetrachloride isotherm would be modified. One infers therefore that the water has entered the bulk of the solid, presumably by chemical combination, and has left the surface unchanged.

After completion of the carbon tetrachloride run and outgassing at 25°, point *F* was again reached; the water isotherm was continued [H_2O(*ib*)] and it was of the usual type. On the conclusion of the water run, the sample was outgassed at 25° so as not to remove the " retained " water; the ensuing carbon tetrachloride isotherm [CCl_4(iii)] was lower than both CCl_4(i) and CCl_4(ii), showing that the water treatment, when carried beyond *F*, *had* diminished the surface area. At the conclusion of this isotherm the sample was evacuated at 25° to get rid of all the carbon tetrachloride, and then at 85° to remove retained water. A carbon tetrachloride isotherm determined immediately afterwards [CCl_4(iv)] was identical with CCl_4(iii). Thus the diminution in area, brought about by water treatment beyond *F*, is not affected by the presence or absence of " retained " water. The shape of *BC* is similar to that of a Type II isotherm; but the shape of *CD* and the decrease obtained in *S* suggest that something other than mere physical adsorption of water vapour has occurred along *BCD*.

The final water isotherm [H_2O(ii)] now determined agreed fairly closely with the first water isotherm. The first water treatment, then, did not bring about a significant modification of the solid with regard to its subsequent powers of adsorbing water.

Experiment B, **3**. The sample was prepared by heating gypsum at 700° for 1 hour. The following four isotherms were determined in succession: CCl_4(i)–outgas at 25°–H_2O(i)–outgas at 25°–CCl_4(ii)–outgas at 25°, then 85°–CCl_4(iii). The first two isotherms were of the usual shape, though the adsorption was in each case small, consistently with a highly calcined sample. There was a small, but not negligible, retention of water on outgassing at 25° after H_2O(i). The carbon tetrachloride isotherm determined with the water present [CCl_4(ii)] and the one obtained after its removal [CCl_4(iii)] agreed closely, confirming that retained water does not significantly alter the surface area of the sample.

Discussion.

From an examination of the experimental data obtained in the course of the present research (Parts I—IV) it is concluded that *within the range of temperature studied*, viz., 100—700°, *and under the conditions of preparation already described* (*i.e.*, dehydration " in air " on the thermal balance), the only lattices to be considered are: (*a*) The *gypsum* lattice (cf. Wells, " Structural Inorganic Chemistry," 1945, 370). (*b*) The *hemihydrate* lattice: this has a zeolitic type of structure such that water molecules can enter and leave it without destroying the lattice (cf. Caspari, *Proc. Roy. Soc.*, 1936, *A*, **155**, 41; Feitknecht, *Helv. Chim. Acta*, 1931, **14**, 89); according to Bunn (*J. Sci. Instr.*, 1941, **18**, 70), this zeolite structure is able to persist up to a water content corresponding to $CaSO_4,0{\cdot}67H_2O$. (*c*) The *anhydrite* lattice—an ionic lattice (Caspari, *loc. cit.*).

It is now postulated that a sample obtained by thermal dehydration of gypsum at a given temperature consists of a mixture of lattices (*b*) and (*c*). The proportion of (*c*) increases as the temperature of preparation increases, but even at 500—600° there is still some of (*b*) left. This has also been inferred by Newman and Wells from *X*-ray data (*J. Res. Nat. Bur. Stand.*, 1938, **20**, 825). Since within the range of temperature considered all samples are completely dehydrated, the (*b*) content will represent hemihydrate completely denuded of its water.

An attempt will now be made to justify the hypothesis by reference to the experimental facts adduced in the present paper.

We deal first with the initial steep portion (*AB*): it has been seen that water cannot be present on the surface, and that it must have entered the bulk solid without affecting its area. This is reasonably explained by supposing that along *AB* the hemihydrate is taking up its zeolitic water. The amount of this water gradually falls as the temperature of preparation is increased (Fig. 4, Curve II). On proceeding with the isotherm beyond point *B*, the following characteristics are noted: (i) the adsorption branch *BC* resembles an ordinary B.E.T. Type II isotherm (Brunauer, Deming, Deming, and Teller, *J. Amer. Chem. Soc.*, 1940, **62**, 1723); (ii) the desorption branch is more or less step-like; (iii) some of the water is " retained " at the conclusion of the desorption branch and can only be removed at 80—90°; (iv) the surface area is decreased after adsorption and consequent desorption of water beyond point *B*.

Fact (i) indicates that the primary process occurring along *BC* is physical adsorption. To account for fact (iii) one postulates that a secondary chemical process occurs at the same time as (and more slowly than) the physical adsorption; this is supported by the step-like form of the desorption branch *CD* [fact (ii)]. Furthermore, this chemical change must be such as to decrease the internal area of the sample [fact (iv)], yet it is unable to exert any effect on the process occurring along *AB*, already referred to. The most likely explanation seems to be this: the hemihydrate formed along *AB* physically adsorbs some water [fact (i)], which then in part combines to form dihydrate [fact (ii)]. The formation of dihydrate at crystallite

boundaries could cement neighbouring crystallites together in such a way as to seal off portions of the surface of the crystallites so that carbon tetrachloride molecules could no longer reach them. On desorption the cementing effect would remain, but the lattice channels through which *water* molecules are able to enter and leave would be unaffected.

The first, very sharp step on the desorption branch may originate in the dissociation $CaSO_4.2H_2O \rightleftharpoons CaSO_4.\frac{1}{2}H_2O + 1\frac{1}{2}H_2O$, in which equilibrium has not been properly attained (for if it had been attained, the step would be absolutely vertical). The second sharp fall is difficult to explain.

The anhydrite present does not seem to be affected by the water treatment: in a repeat run the height *AB* was not increased, nor was the shape of the branch *BC* noticeably altered. If the anhydrite were to react with water during the water treatment represented by *BCD*, giving hemihydrate or gypsum, then in the repeat run the amount of hemihydrate would be increased and the curve *BCD* correspondingly raised.

It now remains to discuss the way in which the proportions of the different solids vary with the temperature of preparation. For this, reference must be made to the curves of surface area against temperature of preparation, given in Part I (Fig. 2). With nitrogen and with carbon tetrachloride there is a maximum at 180—190°, and a very flat maximum at 280—450°; and with oxygen a similar maximum at 180—190° and a much sharper one at *ca.* 300°. The results of Parts III and IV suggest that the first maximum corresponds to the phase change involved in the reaction gypsum ⟶ hemihydrate + water. The second, very flat, maximum is believed to originate in the reaction hemihydrate ⟶ anhydrite + water, together with the sintering of the anhydrite formed. As judged from Fig. 4, some hemihydrate persists up to *ca.* 500°. From 500° to 700°, sintering of the anhydrite predominates.

The variation of the heights x_{AB} and x_{AD} with the temperature of calcination may now be re-examined. The former quantity is plotted against temperature in Fig. 4. Between 100° and 230°, x_{AB} is fairly close to the value required for the composition of the hemihydrate, $CaSO_4.\frac{1}{2}H_2O$. This supports the view already put forward that over the temperature range of 100—230° the product of dehydration consists almost entirely of the hemihydrate denuded of its water. The fall in x_{AB} setting in at about 230° denotes a decreasing proportion of hemihydrate, and with it a corresponding increase in the proportion of anhydrite. The data for the change in surface area brought about by water treatment, also plotted in Fig. 4 (Curve I), are in substantial agreement with this interpretation. Below 230° the curve is irregular, but above it there is close correlation between the curve showing the ratio S_I/S_{II} and the curve for x_{AB} (Curve II, cf. also Part IV, Fig. 3). This is to be expected from the postulate that the anhydrite is inert and that it is only the (dehydrated) hemihydrate that reacts with water. (The irregularity below 230° is probably due to the fact that the water isotherms were taken up to various pressures and for various times; thus the extent of the cementing process would vary from experiment to experiment, so that successive experiments are not strictly comparable in this regard; this effect would, of course, diminish as the content of the hemihydrate decreased.)

The fact that *D* lies above *B* suggests that the entry of water into the lattice, although rapid at first, becomes slower as the process nears completion, *i.e.*, whilst the branch *BCD* is being traced out. This deceleration would come about if, for example, there were parts nearly sealed off by anhydrite, so that penetration there would be slow.

The work was carried out at University College, Exeter.

University College, Exeter.
National Coal Board Central Research Establishment,
Stoke Orchard, Nr. Cheltenham, Glos.

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648. *The Dehydration of Gypsum. Part IV.* The Heat of Immersion, Heat of Hydration, Specific Gravity, Sedimentation Volume, and Bulk Density of the Dehydration Products.*

By S. J. Gregg and E. G. J. Willing.

The quantities enumerated in the title of this paper have been measured on samples of gypsum dehydrated at a succession of temperatures between 110° and 700°. The heat of immersion, the sedimentation volume, and the "tapped" bulk volume all show one maximum in the region of 180° and another in the region of 300°. The heat of hydration falls monotonously as temperature increases, and probably provides a measure of the proportion of "hemihydrate" lattice present in the solid.

The results in the main substantiate the conclusions drawn from the work of Parts I—III and summarised in Part III.

In Parts I—III, the surface area and the chemical nature, of the product formed by the thermal dehydration of gypsum at a series of temperatures have been studied by means of the adsorption of vapours. In the present work the products have been examined by reference to a number of other properties which might be expected to provide supporting evidence. The heat of immersion (in carbon tetrachloride) should give fairly direct, and the bulk volume and the sedimentation volume rather indirect, information as to the variation of the surface area of the solid; the specific gravity and the heat of hydration should give some information as to the chemical and physicochemical nature of the solid phases present.

Experimental.

Materials.—The gypsum was from the batch used in Parts I—III, and was sieved to 40–80 mesh. The dehydrated samples were prepared on the thermal balance in the manner described in Part I. After calcination, the sample was kept in a desiccator over phosphoric oxide until used. All the determinations on a given sample were carried out within 24 hours of its preparation.

The carbon tetrachloride (May and Baker's; boiling range 76—77·5°) was dried over phosphoric oxide. The methyl alcohol (May and Baker's "Commercial," >99% pure) was dried in a manner similar to that given by Lund and Bjerrum (*Ber.*, 1931, **64**, 210): it was kept over magnesium turnings for several days and was then refluxed for 2—3 hours. It was then distilled and the fraction of b. p. 65—66° was collected. The decalin (B.D.H.) was a mixture of the *cis*- and the *trans*-form; it was purified by shaking it with concentrated sulphuric acid till no further tarry matter was removed, and then shaken with alkali, washed with water, dried ($CaCl_2$ and P_2O_5), and distilled, the fraction of b. p. 182—183° being collected. The ethylbenzene (B.D.H.) was dried over phosphoric oxide.

All the liquids were boiled just before use to expel dissolved air.

Apparatus and Procedure.—Heat of immersion in carbon tetrachloride (H_L, *cal. g.*$^{-1}$). The heat of immersion of a solid in an inert liquid (*i.e.*, one that neither reacts with nor dissolves the solid) is known to give a measure of the surface area of the solid (Bangham and Razouk, *Proc. Roy. Soc.*, 1938, *A*, **166**, 572). Indeed, in those cases where the surface is energetically uniform, H_L is proportional to the surface area S cm.^{2} of a given material; for then $H_L = hS$, where h is the heat of immersion per cm.^{2} of the material. In general, the value of h would vary from one substance to another and also from specimen to specimen of a given substance; the latter variation would arise from difference in pretreatment of the specimens and might be expected to be smaller, as a rule, than the former.

Carbon tetrachloride may be regarded as "inert" towards the dehydration products of gypsum. In the present study the heat of immersion of each sample in carbon tetrachloride was determined by means of a calorimeter of special design, to be described elsewhere by Gregg and Hill. It consists essentially of two cylindrical Dewar flasks (of 300 c.c. capacity), *A* and *B*, set in holes in a large aluminium block. A thermel of 16 thermocouples has its "cold" junctions in flask *A* and its "hot" junctions in flask *B*, each set of junctions being mounted on a copper holder. The sample (previously outgassed at 90°) was contained in a sealed-off bulb, and this was placed in a bulb-holder in flask *B*. Connections for the thermel are taken off to a sensitive galvanometer; and an electrical heating coil is mounted, also in flask *B*, for calibration purposes. Each flask contained 30 c.c. of carbon tetrachloride. After insertion of the bulb with its sample, the calorimeter (which was set in a large air-thermostat) was left overnight to settle down. Next morning, readings of the galvanometer were taken for an hour or so to check that they were nearly or quite constant, and the bulb was then broken by a breaker rod. Readings were continued for a further hour or so, to enable cooling corrections to be made; and finally the electrical calibration was performed. Agreement of duplicates to within 0·02 cal. g.$^{-1}$ was usually obtained. The results are plotted as H_L against temperatures of preparation in Fig. 1 (Curve I).

Bulk volume of a solid. This is the volume V occupied by 1 g. of the solid when it is packed in an arbitrary but standard manner. In general, V is made up of: (*a*) V_s, the volume of the solid material itself; (*b*) V_b, the volume of the macro- and micro-pores in the solid, including those of molecular

* Part III, preceding paper.

dimensions; and (*c*) V_v, the space between the individual grains (the "voidage"). The aim of the technique used in measuring is to ensure that the variation of V_v shall be as small as possible. The value of V will then give an approximate measure of $(V_s + V_b)$, *i.e.*, of V_b itself, if V_s is known or can be estimated.

In the present study, a portion (*ca.* 3 g.) of the sample which had been previously sieved was weighed into a 10-c.c. measuring cylinder provided with a stop-cock, and was outgassed at 80—90° for 1—2 hours. It was then mechanically tapped for 15 minutes (*ca.* 500 taps) by a device which will be described elsewhere. Duplicates agreed to 1—2%.

In Fig. 1 the results are plotted as V against temperature of preparation (Curve III).

FIG. 1.

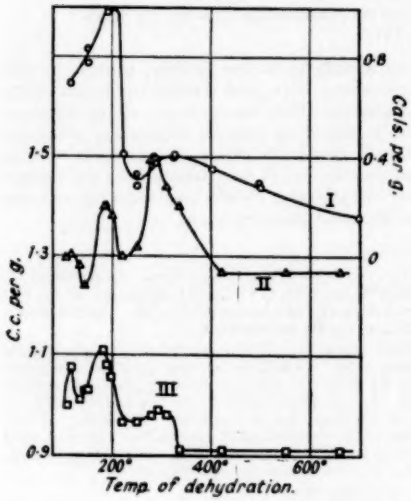


FIG. 2.

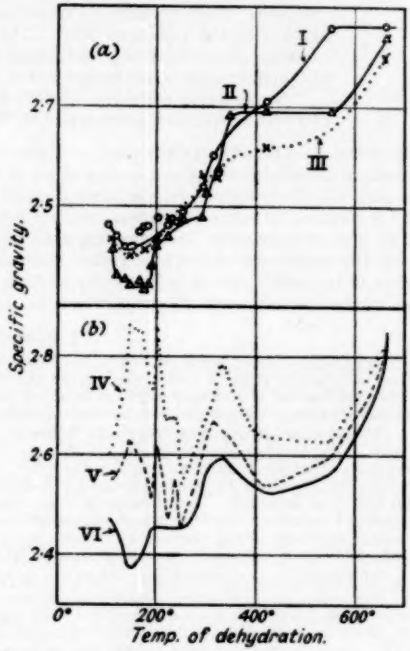


FIG. 1.

Some properties of dehydrated gypsum, plotted against the temperature of dehydration.

I. *Heat of immersion in carbon tetrachloride (use right-hand scale).* II. *Sedimentation volume in carbon tetrachloride (use left-hand scale).* III. *"Tapped" bulk volume (use left-hand scale).*

FIG. 2.

The specific gravity (s.g.) of dehydrated gypsum, plotted against the temperature of dehydration.

I, ○. *s.g. in carbon tetrachloride.* II, △. *s.g. in decalin.* III, ×. *s.g. in ethylbenzene.* IV. *s.g. after immersion for 24 hours in methyl alcohol.* V. *s.g. after immersion for 2 hours in methyl alcohol.* VI. *s.g. after immersion for 10 minutes in methyl alcohol.*

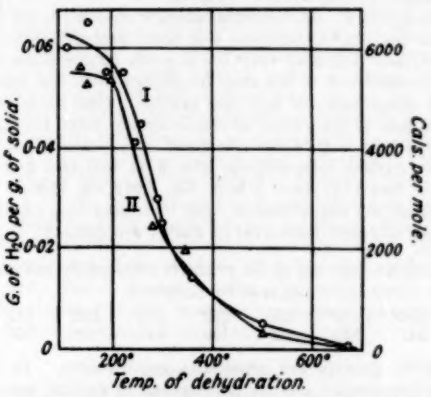
Sedimentation volume in carbon tetrachloride (V_L). The sedimentation volume of a solid in a liquid is the volume occupied by the particles of a suspension after settling (cf. Bloomquist and Shutt, *Ind. Eng. Chem.*, 1940, **32**, 827). It might be expected to run more or less parallel to the bulk volume for a series of related solids (such as a calcination series). Whether V_L depends on the nature of the liquid used is a matter of controversy, but there are good grounds for supposing that it does so depend (cf. Willing, to be published).

The technique of measurement was simple. The weighed sample (*ca.* 3 g.) was introduced into a 10-c.c. measuring cylinder and thoroughly mixed with dry carbon tetrachloride by shaking; after any solids adhering to the walls of the cylinder had been washed down with more carbon tetrachloride, the cylinder was tightly corked, and the solid allowed to settle for 24 hours. The volume could then be read with ease and accuracy. The plot of V_L against temperature of preparation is given in Fig. 1, Curve II.

The specific gravity, ρ, in various liquids. It is well known that the specific gravity of finely divided solids varies according to the liquid in which the solid is immersed for the determination, and various theories have been put forward to account for the effect. The important factors appear to be (*a*) the incomplete penetration of the liquid into the ultrafine pores, and (*b*) the adsorption of the liquid by the solid. Factor (*a*) will tend to *raise* the specific volume, V_ρ ($=1/\rho$); it will exhibit itself as a "drift," *i.e.*, as a slow increase in specific gravity, or a decrease in specific volume, with time. Factor (*b*) will—by causing the liquid molecules to be more tightly packed at the solid–liquid interface than in the bulk of the liquid—tend to *lower* the specific volume.

The effect of (*b*) will be difficult to predict quantitatively from theoretical considerations, but it will in general be small. Measurements of V_ρ should accordingly throw useful light on the pore structure of the solid; and with liquids whose molecules are large enough to render penetration unimportant, the value of V_ρ should give some information as to the chemical nature of the solid phases present (by comparison with standard values). The experimental method used was similar to that described by Cude and Hulett (*J. Amer. Chem. Soc.*, 1920, **42**, 391). A small soda-glass bulb containing 0·5—1 g. of the sample was outgassed for *ca.* 2 hours at 85°, and weighed in air. The tip was then broken off under the surface of the liquid (by use of a breaking device) and the bulb was weighed under the liquid by suspending it in a sling from the hook of a balance; these weighings were taken after 10 minutes, 2 hours, and 24 hours. Finally, weighings of the empty bulb in air were taken both with and without the tip. From the four weighings the specific gravity of the solid is readily calculated (cf. Gregg and Sing, *J. Phys. Colloid Chem.*, 1951, in the press). Slow penetration effects reveal themselves as a "drift" in the density with time.

FIG. 3.



The "retained" water and the heat of hydration of dehydrated gypsum, plotted against the temperature of dehydration.

Curve I: "Retained" water (use left-hand scale). Curve II: Heat of hydration (use right-hand scale).

The specific gravities of the four liquids were determined by the same method, powdered calcite being used in place of the powder. The results (given as specific gravities referred to water at 4°) are: methyl alcohol, 0·787; carbon tetrachloride, 1·600; decalin, 0·870; ethylbenzene, 0·800 (all at the working temperature of 22·5° ±0·1°).

Results.—With decalin (molar volume 160 c.c.) and with ethylbenzene (molar volume 124 c.c.), no drift in density was noted. With carbon tetrachloride there was a slight drift between 10 minutes and 2 hours, but none between 2 and 24 hours; and with methanol large drifts were obtained (except with the most sintered sample, the 680° one). This would seem to show that there are pores present having a diameter comparable with that of the methyl alcohol molecule, and a few having a diameter of the same order as the carbon tetrachloride molecule. (But the possibility that the drift with methanol is due to slow reaction of the solid with traces of water cannot be entirely ruled out.) The values of ρ with decalin, ethylbenzene, and carbon tetrachloride respectively are plotted against the temperature of preparation in Fig. 2*a*. The methanol results are plotted separately in Fig. 2*b*, and the considerable drift is readily seen. The "10-minute" value should be the most comparable with the ρ values of other liquids, whether penetration or reaction is the cause of the drift.

Heat of hydration. Since anhydrite does not react with water in a reasonable space of time, it was thought likely that measurement of the heat evolved when the sample is mixed with excess of water would give an indication of the hemihydrate content of the sample.

For the experimental determination an improved form of ice calorimeter was used, details of which will be published elsewhere. The sample in its bulb was broken under the surface of water by a breaking-rod. Readings of the mercury in the capillary of the calorimeter were then taken every few minutes. Unfortunately, owing to lack of time, duplicates could not be obtained except in two cases, where they agreed to within *ca.* 0·3 cal. $g.^{-1}$. (For most samples the heat of hydration was some 40 cal. $g.^{-1}$.)

The rate of evolution of heat was rapid at first but after 20 minutes it had decreased greatly and after 2 hours was very small; accordingly, it was decided to take the heat evolved in the first 2 hours as the heat of hydration.

The results, calculated as calories per mole of $CaSO_4$, are plotted against temperature of preparation in Fig. 3 (Curve II). In the same diagram are plotted the values of the amount of " retained " water determined in Part III (Figs. 1 and 3), which, it was suggested, is a measure of the hemihydrate content of the sample. As will be seen, the two curves agree remarkably closely (with proper adjustment of the scales of ordinates); and this supports the hypothesis that both the retained water content and the heat of hydration are measures of the hemihydrate content of a sample.

Discussion.

The heat of immersion, the sedimentation volume, and the bulk volume, when plotted against temperature of calcination, all show one maximum at about 180° and another in the region of 300°. These results are in substantial agreement with those of Parts I, II, and III, and they indicate a maximum " activity " in samples prepared at those temperatures. From the very nature of the sedimentation volume and of the bulk volume, one would not expect their curves to coincide in detail with that of surface area against temperature; for, though in general V_L and V both increase with increasing S, exact proportionality would certainly not be expected.

At first sight, one might perhaps expect such coincidence for the heat of immersion curve, since H_L is a direct measure of S. However, as already indicated, the proportionality constant h (— heat of immersion per cm.^{2} of surface) will most probably differ for the anhydrite and the hemihydrate lattice, and will also vary for a given lattice according to the temperature of preparation. Unfortunately, it is not easy to predict even the sense of the variation of h, much less its absolute magnitude for any one sample. One must rest content with noting that the order of magnitude of the values in the following table for the heat evolved per cm.^{2} are reasonable by comparison with those obtained with other solids; *e.g.*, barium sulphate and titanium dioxide in carbon tetrachloride give h as 220 and 240 erg cm.$^{-2}$, respectively, according to Harkins and Boyd (*J. Amer. Chem. Soc.*, 1942, **64**, 1190). (The values in the table have been calculated from the experimental heat of immersion, on the assumption that the areas calculated from the nitrogen isotherms in Part I are correct.)

Heat of immersion per cm.^{2} (h) *of the products obtained by dehydrating gypsum at various temperatures.*

Temp.	116°	152°	188°	222°	250°	287°	325°	400°	500°	700°
h (ergs cm.$^{-2}$)	347	330	330	159	117	138	167	146	134	268

The results for specific gravity are somewhat inconclusive. In the region of 150—180° there is a minimum in the specific gravity determined in carbon tetrachloride, in decalin, in ethylbenzene, and in methyl alcohol (" 10-minutes "), and this would correspond to a maximum in the specific volume of the solid; and this in turn would seem to correspond to the maximum in the surface area, S, determined by adsorption (Parts I and II), and in the sedimentation volume, V_L, the bulk volume, V, and the heat of immersion, H_L (this Part). It is difficult to formulate any detailed interpretation of the numerical values of the minimum density, however, for not only does ρ differ according to the liquid used, but there is wide variation in the values quoted in the literature for $CaSO_4.0{\cdot}5H_2O$ (whence ρ for the dehydrated hemihydrate would have to be calculated). This latter circumstance no doubt arises from the considerable sensitivity of the specific gravity of hemihydrate to conditions of preparation. There is no second maximum in ρ corresponding to the maxima found in S, V_L, V, and H_L, in the region of 300°.

It is of interest that the value of ρ for the 680° sample, *viz.* 2·8—2·86, is not far from the standard value for anhydrite (2·92), and the fall in ρ in Fig. 2*a* as temperature increases from 200° to 680° is not incompatible with the view put forward in Part III that over this range the content of anhydrite is growing at the expense of the content of dehydrated hemihydrate. The presence of the flat portion of the graphs II and III of Fig. 2*a* taken together with the data for methyl alcohol in Fig. 2*b*, suggest that the detailed interpretation is likely to be a complex one, however.

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University College, Exeter.
National Coal Board Central Research Establishment,
Stoke Orchard, Nr. Cheltenham, Glos.

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649. *The Electrolytic Dissociation of Magnesium Sulphate and Lanthanum Ferricyanide in Mixed Solvents.*

By Helen S. Dunsmore and J. C. James.

Conductivity measurements are reported for magnesium sulphate in water, dioxan–water mixtures, and glycine solutions, and for lanthanum ferricyanide in glycine solutions. Dissociation constants have been derived, and it is shown that a simple electrostatic explanation will account for the variation of dissociation constant with dielectric constant. A comparison is drawn between ion-pair sizes as calculated by Stokes's law and by Bjerrum's method.

Numerous measurements have been made of the conductivities of salts in non-aqueous and in mixed solvents, and deviations from the limiting Onsager equation have in many cases been satisfactorily accounted for by the assumption of incomplete dissociation. Dissociation constants can be calculated, and in general it would appear that when ion-pairs are formed from large spherical ions, or from large and stably solvated ions, variation of dissociation constant with dielectric constant may be accounted for satisfactorily by Bjerrum's treatment (*Kgl. Danske Vidensk. Selskab.*, 1926, **7**, No. 9). Very few measurements appear to have been made in media of dielectric constant higher than that of water, however, and for this reason the present work has been carried out. It has recently been shown by Monk (*Trans. Faraday Soc.*, 1950, **46**, 645) that the conductivity of potassium chloride in aqueous glycine solutions is in agreement with the Onsager equation and it appeared to be of interest to examine the behaviour of electrolytes of higher valency type in such solutions. Magnesium sulphate was chosen as a suitable 2–2-valency type salt, not subject to hydrolysis, and conductivity measurements have been made on solutions in water, and in dioxan–water and glycine–water mixtures. Measurements have also been made on glycine–water solutions of lanthanum ferricyanide, a 3–3-valency type salt, for which the conductivities in water and in mixed solvents of lower dielectric constant than water have been reported in earlier papers (Davies and James, *Proc. Roy. Soc.*, 1948, *A*, **195**, 116; James, *J.*, 1950, 1094). An exploratory study of conductivities in urea–water solutions was made, but drift in solvent resistance, presumably due to hydrolysis, was too great for accurate measurements to be obtained.

Experimental.

Glycine was dissolved, filtered, and recrystallised thrice from conductivity water and finally dried to constant weight over potassium hydroxide *in vacuo*. Dioxan (" purissimus " grade) was purified by prolonged refluxing with sodium and fractional distillation (Kraus and Vingee, *J. Amer. Chem. Soc.*, 1934, **56**, 513). Magnesium sulphate (" AnalaR ") was recrystallised from water and dried over the partially dehydrated salt. Lanthanum ferricyanide, $LaFe(CN)_6.5H_2O$, was prepared and analysed as described by Davies and James (*loc. cit.*).

The conductivity equipment and experimental technique used have been described elsewhere (Davies, *J.*, 1937, 432; James, *loc. cit.*). Concentrations were determined by weight, and volume concentrations were calculated from the densities of the mixed solvents, it being assumed that the small amount of salt added did not appreciably alter the density. All measurements were made at 25° ±0·005°. Measurements of pH were made by the glass-electrode method, by using the " reproducible liquid junction " apparatus of Smith and Speakman (*Trans. Faraday Soc.*, 1948, **44**, 1031), standardisation being effected with suitable buffer solutions, as recommended by Hitchcock and Taylor (*J. Amer. Chem. Soc.*, 1937, **59**, 1812).

Dielectric constants for aqueous dioxan solutions were obtained from the data of Åkerlöf and Short (*ibid.*, 1936, **58**, 1241), densities from those of Hovorka (*ibid.*, p. 2264) and of Geddes (*ibid.*, 1933, **55**, 4832), and viscosities from those of Owen and Waters (*ibid.*, 1938, **60**, 2371) and of Geddes (*loc. cit.*). Densities for aqueous glycine solutions were obtained from Wyman's data (*ibid.*, 1934, **56**, 536); dielectric constants and viscosities were interpolated from the data listed by Monk (*loc. cit.*).

Discussion.

Aqueous Magnesium Sulphate Solutions.—Although Owen and Gurry (*ibid.*, 1938, **60**, 3074) found that their conductivity data for aqueous zinc sulphate and copper sulphate solutions required appreciable correction for hydrolysis, magnesium hydroxide is relatively a much stronger base (cf. Davies, *J.*, 1951, 1256) and no hydrolysis is to be expected in magnesium sulphate solutions. Calculations based on Stock and Davies's value of $K = 2{\cdot}6 \times 10^{-3}$ for the second dissociation constant of magnesium hydroxide (*Trans. Faraday Soc.*, 1948, **44**, 856),

the carbon dioxide content of the solutions (as determined from the specific conductivity of the solvent), and the pH's of the solutions (normally about 6·0) confirm this view.

TABLE I.

Conductivity of aqueous magnesium sulphate solutions.

Run	$10^6K_{H_2O}$	10^4c	$10^2c^{\frac{1}{2}}$	Λ	pK	Run	$10^6K_{H_2O}$	10^4c	$10^2c^{\frac{1}{2}}$	Λ	pK
1	0·251	1·6196	1·2726	127·31	2·216	2	0·264	1·7021	1·3046	127·11	2·225
		3·2672	1·8075	124·27	2·232			3·9871	1·9968	123·13	2·237
		5·3847	2·3204	121·34	2·222			6·1798	2·4859	120·33	2·226
		8·5946	2·9316	117·85	2·211			8·5401	2·9223	117·89	2·214
		12·011	3·4656	114·92	2·200			11·194	3·3456	115·50	2·207
		16·759	4·0937	111·61	2·184			14·393	3·7937	113·14	2·193
								17·692	4·2062	111·02	2·183

Results for aqueous magnesium sulphate solutions at 25° are given in Table I. Combination of the value $\Lambda_0(Mg^{"}) = 53{\cdot}06$, given by Shedlovsky and Brown (*J. Amer. Chem. Soc.*, **1934**, **56**, 1066), with Jenkins and Monk's value of $\Lambda_0(SO_4^{"}) = 80{\cdot}00$ (*ibid.*, **1950**, **72**, 2695) leads to the value $\Lambda_0 = 133{\cdot}06$ for the conductivity of magnesium sulphate at infinite dilution. The limiting Onsager equation for magnesium sulphate then becomes $\Lambda = 133{\cdot}06 - 242{\cdot}11I^{\frac{1}{2}}$, where I is the ionic strength. The results have been plotted in Fig. 3, and it can be seen that magnesium sulphate resembles other 2–2-valency type electrolytes in that the conductivities, even at high dilutions, show marked departure from the limiting Onsager slope. If these deviations are attributed to incomplete dissociation, then α, the degree of dissociation, may be calculated from the Onsager relation $\alpha = \Lambda/\{133{\cdot}06 - 342{\cdot}39(\alpha c)^{\frac{1}{2}}\}$, where c is the concentration in g.-equiv./l. Thermodynamic dissociation constants have been calculated for each point from the equation

$$\log K = -pK = \log [\alpha^2 c/2(1-\alpha)] - 5{\cdot}760(\alpha c)^{\frac{1}{2}}$$

and are given in Table I. In this way the mean value $pK = 2{\cdot}21 \pm 0{\cdot}015$ was obtained.

TABLE II.

	0·1 Molal glycine			0·25 Molal glycine			0·5 Molal glycine		
$c \times 10^4$	Λ	Corr.	$\Lambda_{Corr.}$	Λ	Corr.	$\Lambda_{Corr.}$	Λ	Corr.	$\Lambda_{Corr.}$
(A) *Conductivity of lanthanum ferricyanide in glycine–water mixtures.*									
2	130·60	0·34	130·94	128·61	0·73	129·34	125·03	0·87	125·90
3	123·59	0·27	123·86	122·69	0·50	123·19	120·41	0·70	121·11
4	118·05	0·23	118·28	117·98	0·41	118·39	116·72	0·61	117·33
5	113·63	0·20	113·83	114·10	0·35	114·45	113·65	0·44	114·09
6	110·00	0·18	110·18	110·87	0·31	111·18	110·85	0·39	111·24
7	106·84	0·17	107·01	108·06	0·28	108·34	108·52	0·36	108·88
8	104·14	0·16	104·30	105·52	0·25	105·77	106·46	0·33	106·79
9	101·80	0·15	101·95	—	—	—	104·48	0·30	104·78
10	99·64	0·14	99·78	—	—	—	102·67	0·28	102·95
(B) *Conductivity of magnesium sulphate in glycine–water mixtures.*									
2	123·86	0·20	124·06	120·20	0·26	120·46	115·35	0·52	115·87
3	122·10	0·17	122·27	118·82	0·21	119·03	114·22	0·44	114·66
4	120·65	0·14	120·79	117·66	0·19	117·85	113·25	0·38	113·63
5	119·35	0·13	119·48	116·65	0·17	116·82	112·40	0·34	112·74
6	118·23	0·12	118·35	115·71	0·15	115·86	111·62	0·31	111·93
7	117·21	0·11	117·32	114·86	0·14	115·00	110·92	0·29	111·21
8	116·30	0·10	116·40	114·07	0·14	114·21	110·25	0·27	110·52
9	115·44	0·10	115·54	113·33	0·13	113·46	109·63	0·26	109·89
10	114·64	0·09	114·73	112·61	0·12	112·73	109·04	0·24	109·28

(C) *Conductivity of more concentrated lanthanum ferricyanide solutions.*

0·1 Molal glycine				0·25 Molal glycine				0·5 Molal glycine			
$c \times 10^4$	Λ	Corr.	$\Lambda_{Corr.}$	$c \times 10^4$	Λ	Corr.	$\Lambda_{Corr.}$	$c \times 10^4$	Λ	Corr.	$\Lambda_{Corr.}$
22·197	84·05	0·09	84·14	21·024	87·44	0·20	87·64	25·088	87·49	0·23	87·72
33·744	76·30	0·07	76·37	30·606	80·60	0·16	80·76	35·177	81·83	0·19	82·02
36·023	75·22	0·07	75·29	37·449	77·19	0·15	77·34	41·889	78·96	0·18	79·14

(D) *Conductivity of magnesium sulphate in dioxan–water mixtures.*

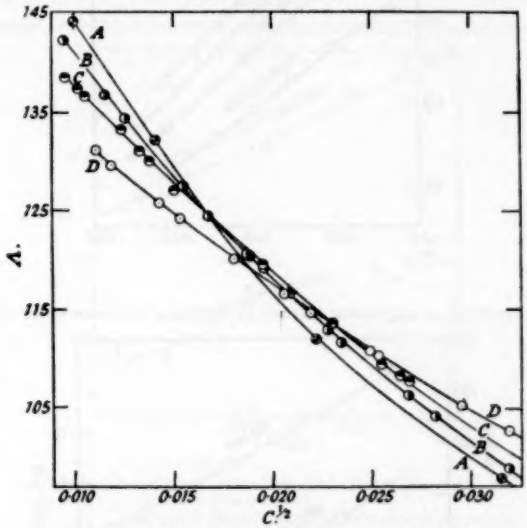
	10% (w/w)	20% (w/w)		10% (w/w)	20% (w/w)		10% (w/w)	20% (w/w)
$c \times 10^4$	dioxan, Λ	dioxan, Λ	$c \times 10^4$	dioxan, Λ	dioxan, Λ	$c \times 10^4$	dioxan, Λ	dioxan, Λ
2	104·73	84·58	5	99·38	78·02	8	95·58	73·52
3	102·66	82·01	6	97·98	76·31	9	94·51	72·34
4	100·93	79·91	7	96·72	74·82	10	93·53	71·22

Owen and Gurry (*loc. cit.*) have stated that with aqueous zinc and copper sulphate solutions, values obtained for K were appreciably dependent upon the manner in which Λ was assumed to approach the limiting value. With the present results, calculation of α from Shedlovsky's equation (*J. Franklin Inst.*, 1938, **225**, 739), $\Lambda = \alpha\{\Lambda_0 - b(\Lambda/\Lambda_0)(\alpha c)^{\frac{1}{2}}\}$, gave a mean value of $pK = 2{\cdot}26_6 \pm 0{\cdot}007$. Where comparisons are made of dissociation constants obtained by consistent use of one extrapolation method, as in the present work, it seems unlikely that any marked error can be introduced by this slight dependency of K on the extrapolation method used.

Methods for the direct extrapolation of conductivity data for weak electrolytes have been put forward by Davies (*J.*, 1933, 645) and by Shedlovsky (*loc. cit.*). The Davies extrapolation gives $\Lambda_0 = 132{\cdot}9$; the Shedlovsky extrapolation is rather more nearly linear and leads to $\Lambda_0 = 132{\cdot}8$. Both are in good agreement with the "independent" value $\Lambda_0 = 133{\cdot}06$.

FIG. 1.

The conductivity of lanthanum ferricyanide in water and in glycine–water mixtures.



A. *Water (from data of Davies and James,* loc. cit.).
B. 0·1M-*Glycine solution.*
C. 0·25M-*Glycine solution.*
D. 0·5M-*Glycine solution.*

Mixed Solvents.—The results are given in Table II, interpolated values being given for the more dilute solutions, to save space.

A careful study of the solvent correction to be applied to conductivity data for unhydrolysed salts in glycine solutions has been made by Monk (*loc. cit.*), who concludes that a simple subtraction of the initial glycine solution conductivity represents the true solvent correction. Since the mobilities of solute ions are slightly lowered by the presence of solvent ions, a correction, $\Delta\Lambda$ is required for this interionic attraction effect (Davies, *Trans. Faraday Soc.*, 1929, **25**, 129), and has been calculated from $\Delta\Lambda = b\{(I + I_0)^{\frac{1}{2}} - I^{\frac{1}{2}}\}$, where b is the Onsager slope and I_0 is the ionic strength of the glycine solution. Values for I_0 were obtained from the pH's of the glycine solutions and the known ionisation constants of glycine, as described by Monk (*loc. cit.*), and the true ionic strength of the solute ions, I, was calculated by a method of successive approximations. Equivalent conductivities at infinite dilution and values for α, the degree of dissociation, were obtained by Davies's extrapolation method (*loc. cit.*), uncorrected conductivity values being used; approximate values for I could then be found. Conductivity corrections, $\Delta\Lambda$, were then calculated from the above equation, and the corrected conductivity values used to derive more accurate values for Δ_0, α, and I. Approximations were

continued in this way until steady values for Λ_0, α, I, and $\Delta\Lambda$ were obtained. These corrections are given in Table II, and also the corrected conductivity values finally obtained.

The pH changes caused by addition of magnesium sulphate or lanthanum ferricyanide to glycine solutions were never greater than 0·05 pH unit, about the order to be expected as a result of the alteration in ionic strength.

FIG. 2.

The conductivity of magnesium sulphate in water, and in glycine–water mixtures.

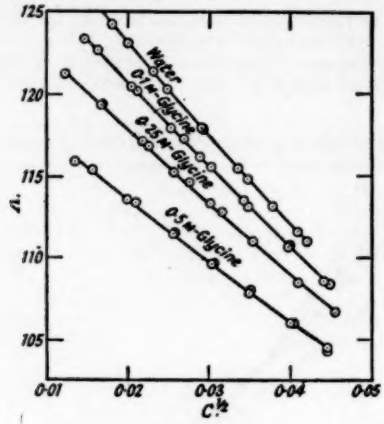
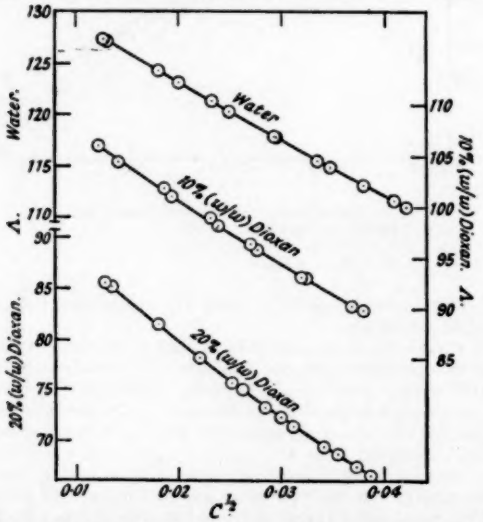


FIG. 3.

The conductivity of magnesium sulphate in water and in dioxan–water mixtures.



Results for lanthanum ferricyanide in glycine–water mixtures are shown in Fig. 1, together with the results in water given by Davies and James (*loc. cit.*). The curves show an interesting transposition in order with increasing salt concentration, probably as a result of the opposing influences of the viscosity and dielectric constant of the medium. At very low concentrations (<0·0004N.) the effect of viscosity predominates, and conductivities, in consequence, decrease

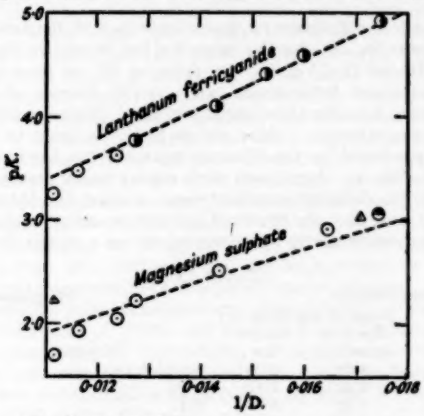
with increasing glycine concentration (*i.e.*, with increase in viscosity). At higher concentrations (>0·0006N.) the effect of the increase in dissociation, caused by increase in dielectric constant, becomes predominant and conductivities increase with increase in glycine concentration.

Results for magnesium sulphate in water, glycine–water, and dioxan–water mixtures are given in Figs. 2 and 3. The extent of ion association in salt solutions is, in general, proportional to the valency product of the ions concerned and is much smaller with the 2–2-valent magnesium sulphate than with the 3–3-valent lanthanum ferricyanide. In consequence, the curves for magnesium sulphate in glycine solutions do not intersect over the concentration range studied, the decrease in ionic mobilities caused by increasing solvent viscosity outweighing the effect of the increase in dissociation caused by dielectric constant increase. In dioxan–water mixtures, the effect of both viscosity and dielectric constant change is to cause the conductivity to decrease with increase in the dioxan concentration.

We have treated the above data by ascribing deviations from the limiting Onsager equation to ion association and applying the treatment given by Davies for incompletely dissociated

FIG. 4.

Variation of dissociation constant with dielectric constant in mixed solvents.



○ *Present work.*
◑ *Davies and James* (loc. cit.), *James* (loc. cit.).
◓ *James (unpublished work).*
△ *Mason and Shutt* (loc. cit.), *from dielectric-constant data.*

The broken curves have been calculated from the Bjerrum equation, on the assumption of a = 7·20 Å *for lanthanum ferricyanide, and* a = 5·06 Å *for magnesium sulphate, in water.*

electrolytes (*loc. cit.*). For each series of measurements, values of Λ_0 and α have been calculated, corrections, $\Delta\Lambda$, for the interionic attraction effect of the solvent ions on the solute conductivity being derived simultaneously, as described on p. 2927. Thermodynamic dissociation constants have been calculated for each point from the equations

$$\log K = \log [\alpha^2 c/3(1 - \alpha)] + \log f_{\pm}^2 \text{ for lanthanum ferricyanide}$$

and

$$\log K = \log [\alpha^2 c/2(1 - \alpha)] + \log f_{\pm}^2 \text{ for magnesium sulphate}$$

where c is the concentration in g.-equivs./litre. Values for $f_{\pm}$, the mean ionic activity coefficient, were calculated from the limiting Debye–Hückel equation. The mean dissociation constant values obtained are expressed as pK's in Table III, together with related data for the mixed solvents, and in Fig. 4, pK's have been plotted against reciprocal dielectric constants, D^{-1}. Data for lanthanum ferricyanide in dioxan–water mixtures (James, *J.*, 1950, 1094) have also been plotted, for comparison.

Mason and Shutt (*Proc. Roy. Soc.*, **1940**, **A**, **175**, 234) have determined the dielectric constants of dilute solutions of magnesium sulphate in dioxan–water and urea–water solutions at 20°, and have calculated ion-pair dissociation constants from these measurements. Their results in dioxan–water are in good agreement with ours, where comparison is possible (see Fig. 4),

TABLE III.

Solvent	D	$10^3\eta$	Magnesium sulphate Λ_0	$\Lambda_0\eta$	pK	Lanthanum ferricyanide Λ_0	$\Lambda_0\eta$	pK
0·5 Molal glycine ...	89·78	9·49	119·9	1·138	1·699	144·7	1·373	3·252
0·25 ,, ...	86·08	9·21	125·4	1·155	1·938	154·6	1·424	3·473
0·1 ,, ...	80·80	9·05	129·2	1·169	2·054	161·9	1·465	3·621
Water	78·54	8·949	133·06	1·191	2·211	168·9	1·511	3·740
10% (w/w) Dioxan...	69·75	10·9	111·9	1·220	2·512	—	—	—
20% (w/w) Dioxan...	60·79	12·9	9·39	1·213	2·906	—	—	—

but their pK values in urea–water solutions appear to be considerably higher than our values in glycine–water solutions.

Assuming that forces between oppositely charged ions obey the simple Coulomb law, Bjerrum (*loc. cit.*) has shown that the equilibrium constant for an ion-pair should be given by

$$K^{-1} = \frac{4\pi N}{1000}\left(\frac{|z_1z_2|\varepsilon^2}{DkT}\right)^3 . Q(b)$$

where $Q(b)$ is defined by the integral $Q(b) = \int_2^b e^y y^{-4} . dy$, in which $y = |z_1z_2|\varepsilon^2/rDkT$, $b = |z_1z_2|\varepsilon^2/aDkT$, and a is the distance of closest approach of the ions. Values of $Q(b)$ have been tabulated by Bjerrum (*loc. cit.*) for the range $2 \leqslant b \leqslant 15$ and by Fuoss and Kraus (*J. Amer. Chem. Soc.*, **1933**, **55**, 1019) for $15 \leqslant b \leqslant 80$. In water, at 25°, we have for magnesium sulphate, pK = 2·21, and for lanthanum ferricyanide, pK = 3·740 (Davies and James, *loc. cit.*). On substitution of these values into the above equation, the " Bjerrum distances," a, are found to be 5·06 Å and 7·20 Å, respectively. These values being assumed to remain unchanged, the variation of K with D predicted by the Bjerrum equation has been calculated, and is shown by the dashed curves in Fig. 4. Agreement with experimental results is good and there can be little doubt that, over the dielectric-constant range studied, the extent of hydration remains substantially unchanged, and that the observed increase in extent of dissociation with increase in dielectric constant can satisfactorily be accounted for on a simple Coulomb's law basis.

TABLE IV.

Lanthanum ferricyanide Solvent	Radii of ion-pairs (Å): Bjerrum equation	Stokes law	Magnesium sulphate Solvent	Radii of ion-pairs (Å): Bjerrum equation	Stokes law
0·5 Molal glycine	8·32	7·39	0·5 Molal glycine	7·24	6·01
0·25 ,, ...	7·42	7·12	0·25 ,, ...	5·79	5·92
0·1 ,, ...	7·52	6·92	0·1 ,, ...	5·85	5·85
Water	7·20	6·67	Water	5·06	5·75
* 9·67% (w/w) Dioxan	7·17	6·80	10% (w/w) Dioxan	4·84	5·60
* 14·84 ,, ...	7·08	6·58	20% ,, ...	4·53	5·64
* 18·08 ,, ...	7·08	6·51			
* 24·07 ,, ...	7·19	6·67			

* From James's data (*J.*, 1950, 1094).

It is generally assumed that Stokes's law is applicable to the movement of large spherical ions, and that such an ion, of radius r and valency z, acted upon by an electric force $Xz\varepsilon$, would be maintained at a velocity $v = Xz\varepsilon/6\pi\eta r$ in a homogeneous medium of viscosity η. In terms of the limiting ionic mobility, Λ_{io}, at 25°, this equation becomes $r = 8{\cdot}197 \times 10^{-8}z/\Lambda_{io}\eta$ (Harned and Owen, " The Physical Chemistry of Electrolytic Solutions," Reinhold, New York, 1943, p. 184). With a solvated ion it seems probable that the ion and its attached solvent molecules move as a single entity under an applied electric field and that Stokes's law gives a direct measure of primary ionic solvation (Bockris, *Quart. Reviews*, 1949, III, 173). In Table IV, values for the mean diameters, a, of ion-pairs have been obtained by addition of cationic and anionic radii derived from the above equation, it being assumed that the transport numbers of the ions do not change with change in the solvent. Values for a calculated from the Bjerrum equation are given for comparison; agreement between the two methods is very reasonable. An appreciable increase in a occurs in glycine–water solutions, possibly because of solvation by glycine. In dioxan–water mixtures it is probable that water dipoles alone solvate the ions and that dioxan molecules, with their large size and relatively small dipole moment, do not enter the ionic solvation sheaths in the mixed solvents studied.

UNIVERSITY OF GLASGOW.

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650. α-*Methylbenzylamines. Part I.* 3-cyclo*Hexyloxy*-4-*methoxy*-α-*methylbenzylamines.*

By A. McCoubrey.

Attempts to prepare aryl ethers of 3-aminoethyl*cyclo*hexanols have been unsuccessful. Suitable 1 : 3-disubstituted *cyclo*hexane derivatives reverted to *cyclo*hexenes under alkaline or dehydrating conditions. A series of 3-*cyclo*hexyloxy-4-methoxy-α-methybenzylamines has been prepared by standard methods from *iso*acetovanillone.

Until recently there were two molecular models available for a study of the relation between chemical structure and biological activity in the analgesic field (excluding antipyretic analgesics), *viz.*, ethanol and the morphine bases. The contrast between the simple structure of ethanol and the complexity of morphine is striking, and, though there is little evidence to suggest that these two substances exert their analgesic activity by similar modes of action in the body, both are analgesic and euphoriant and cause habituation, indicating some common degree of biological involvement. Many drugs which exert effects in the nervous system, of which analgesics form one aspect, are notable for their simple molecular organisation and, with the above two considerations in mind, a search for a relatively simple molecule imbued with analgesic properties of opiate character seemed a feasible project. When this work was initiated pethidine was undergoing clinical trial and the subsequent work of recent years has made it apparent that almost any dissection of the morphine molecule, provided that the product bears the basic nitrogen atom, will have some degree of analgesic activity (cf. Bergel and Morrison, *Quart. Reviews*, 1948, **2**, 349), though advances in this field have to a large extent depended on the recent development of relatively satisfactory methods for detection of weak analgesic activity in small laboratory animals.

The report of the Committee on Drug Addiction of the U.S. National Research Council (Public Health Suppl., 1938, No. 138) provided the background for basic concepts, and the synthesis of aryl ethers of 3-aminoethyl*cyclo*hexanol was attempted.

Interaction of *m*-methoxyphenylmagnesium bromide and *n*-butyl diethylaminomethyl ether (Robinson and Robinson, *J.*, 1923, **123**, 534) gave *NN*-diethyl-*m*-methoxybenzylamine, also obtained (less satisfactorily) by bromination of methyl *m*-tolyl ether with *N*-bromosuccinimide followed by reaction with diethylamine. Demethylation gave *NN*-diethyl-*m*-hydroxybenzylamine, but debenzylation occurred on catalytic hydrogenation and no nuclear reduction products were isolated.

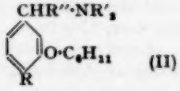
The addition of nitromethane to *cyclo*hex-2-enone gave a nitromethyl*cyclo*hexanone in moderate yield, whereas nitroethane under similar conditions gave a better yield of 3-1′-nitroethyl*cyclo*hexanone. A Nef reaction (*Annalen*, 1894, **280**, 263) then gave 3-acetyl*cyclo*hexanone, the structure of which was demonstrated by dehydrogenation to give *m*-hydroxyacetophenone. Reduction by aluminium *iso*propoxide gave 3-1′-nitroethyl*cyclo*hexanol, whence a Nef reaction led to 3-acetyl*cyclo*hexanol, the phenylurethane of which could be separated into two isomers by fractional crystallisation. 3-Acetyl*cyclo*hexanol was readily converted into the corresponding bromide or iodide but the alkaline conditions of etherification led to loss of hydrogen halide to give 3(?)-acetyl*cyclo*hexene. 3-Acetyl*cyclo*hexanol also gave acetyl*cyclo*hexene in contact with hot acid solutions.

In a third approach dihydroresorcinol was converted into 3-chloro*cyclo*hex-2-enone whence reaction with phenol, catechol, or guaiacol gave the 1-aryloxy*cyclo*hex-2-enones. These substances did not exhibit the typical ketone reactions. The 1 : 2-unsaturation conferred lability on the ether link and attempts to reduce the unsaturated ketone group by various methods gave rise mainly to the products of reductive cleavage; 3-phenoxy*cyclo*hex-2-enone was more labile than the *o*-methoxyphenyl analogue, so that 3-phenoxy*cyclo*hexanol was only obtainable in very poor yield by rapid reduction with sodium and hot alcohol. Catalytic hydrogenation over palladised charcoal, which caused complete cleavage of 3-phenoxy*cyclo*hexenone, slowly reduced the *o*-methoxyphenoxy-compound to (presumably) 3-*o*-methoxyphenoxy*cyclo*hexanone. Completion of the hydrogenation over platinum black gave a moderate yield of 3-*o*-methoxyphenoxy*cyclo*hexanol together with some *cyclo*hexanol and guaiacol. 3-*o*-Methoxyphenoxy*cyclo*hexanol and phosphorus tribromide gave an unstable bromide and attempts to prepare the Grignard reagent of this substance failed. This alcohol

readily gave a phenylurethane; phenyl *iso*cyanate and 3-phenoxy*cyclo*hexanol gave an unsaturated substance and carbanilide.

Attention was next turned to analogous α-methylbenzylamines. *NN*-Diethyl-3-hydroxy-4-methoxybenzylamine could only be obtained in prohibitive yield. *NN*-Diethyl-4-methoxy-3-nitrobenzylamine, readily obtained from 4-methoxy-3-nitrobenzyl chloride and diethylamine, was easily reduced to the amine (contrast the difficult reduction of 4-methoxy-3-nitrobenzyl alcohol; Fishman, *J. Amer. Chem. Soc.*, 1920, **42**, 2298), and the derived diazonium salt readily decomposed on warming (cf. Fishman, *loc. cit.*) but gave *NN*-diethyl-3-hydroxy-4-methoxybenzylamine in very poor yield. The diazonium group could however be replaced by bromine by the usual Sandmeyer procedure (cf. Fishman, *loc. cit.*) (the corresponding iodo-derivative could not be so prepared), but the product did not react at elevated temperatures with sodium or potassium *cyclo*hexyl oxide.

(I)



(II)

Products of the desired structure were eventually obtained from *iso*acetovanillone (I; R = OH). Reduction of its oxime gave (±)-3-hydroxy-4-methoxy-α-methylbenzylamine, which was quite stable in contrast to the isomeric 4-hydroxy-3-methoxy-compound (Moore, *J.*, 1911, **99**, 418). Etherification of the amine with *cyclo*hexyl bromide and alkali did not proceed to a useful extent; nor did that of *iso*acetovanillone with *cyclo*hexanol and zinc chloride in presence of hydrochloric acid (*Chem. Abs.*, 1940, **34**, 1445), probably owing to formation of pyrylium salts by the acetyl group; however, it was effected by very slow addition of methanolic sodium or potassium hydroxide to a refluxing alcoholic solution of the ketone containing excess of *cyclo*hexyl bromide (Klarmann, Gatyas, and Shternov, *J. Amer. Chem. Soc.*, 1931, **53**, 3404)—*cyclo*hexyl chloride failed to react under similar conditions. At the best, *ca.* 40% of the ether was formed; it is probable that the reaction is progressively hindered by the accumulation of the products. 3-*cyclo*Hexyloxy-4-methoxyacetophenone oxime was readily reduced by sodium amalgam to the amine (II; R = OMe; R′ = H; R″ = Me); *N*-derivatives of this amine were obtained by reduction of (I; R = *cyclo*hexyloxy) to the carbinol, conversion into the bromide, and reaction of this with the appropriate amine in benzene. Reduction of the carbonyl group of (I; R = *cyclo*hexyloxy) by sodium in ethanol, or by aluminium *iso*propoxide in xylene, gave a large proportion of low-boiling material, and catalytic methods gave a similar result if the solvent was either methanol or acetic acid. In ethyl acetate however, although the rate of absorption of hydrogen was greatly retarded, very little low-boiling material was produced. At the same time susceptibility to poisoning of the catalyst was markedly increased and samples of the ketone which could not be hydrogenated in ethyl acetate readily absorbed hydrogen in methanol or acetic acid. The alcohol, characterised as the phenylurethane, reacted with phosphorus tribromide to give an unstable bromide which slowly lost hydrogen bromide at room temperature but, when immediately treated with the appropriate amine in benzene, gave the *NN*-di-methyl, -ethyl, -*n*-propyl, and -*n*-butyl and the tetrahydro*iso*quinoline derivatives.

Experimental.

NN-*Diethyl*-m-*methoxybenzylamine*.—(*a*) The Grignard reagent from *m*-bromoanisole (20 g.) and magnesium (2·7 g.) in ether (50 c.c.) was added during 1 hour to *n*-butyl diethylaminomethyl ether (Robinson and Robinson, *loc. cit.*) (22 g.) in ether (50 c.c.). After 12 hours ammonium chloride solution was added and the product extracted with ether. Distillation of the dried ethereal extract gave an oil (10·2 g.), b. p. 132—135°/18 mm., which was converted into the hydrochloride. NN-*Diethyl*-m-*methoxybenzylamine hydrochloride* crystallised from alcohol in needles, m. p. 152° (Found: N, 5·9. $C_{12}H_{19}ON,HCl$ requires N, 6·1%). The *picrolonate* crystallised from alcohol in yellow prisms, m. p. 139° (Found: C, 57·5; H, 6·2; N, 14·6. $C_{12}H_{19}ON,C_{10}H_8O_5N_4,\frac{1}{4}C_2H_6O$ requires C, 57·5; H, 6·3; N, 14·6%).

(*b*) Methyl *m*-tolyl ether (24·5 g.), *N*-bromosuccinimide (36 g.), and benzoyl peroxide (0·3 g.) were heated under reflux in carbon tetrachloride (140 c.c.) for 4 hours. Succinimide was filtered off and the carbon tetrachloride distilled off. The residue, in benzene (100 c.c.), was treated with diethylamine (30 c.c.). After 12 hours diethylamine hydrobromide (7·6 g.) was filtered off and the filtrate extracted with 5*N*-hydrochloric acid. The acid extract was basified with sodium hydroxide and extracted with ether, and the extract dried (K_2CO_3) and distilled, to give the amine (7·5 g., 19%), b. p. 116—120°/6 mm. The acid-insoluble material remaining in the benzene was distilled, to give methyl *m*-tolyl ether (2·0 g.), b. p. 75—82°/16 mm., and a bromo-compound (18·7 g.), b. p. 110—115°/16 mm., shown to be 4-bromo-

3-methylanisole since carboxylation of the derived Grignard reagent gave 4-methoxy-2-methylbenzoic acid, m. p. 177° (Found: C, 65·3; H, 6·3. Calc. for $C_9H_{10}O_3$: C, 65·1; H, 6·0%) (cf. Darzens and Levy, *Compt. rend.*, 1931, **193**, 292).

NN-*Diethyl*-m-*hydroxybenzylamine*.—The foregoing amine (18·6 g.) and hydrobromic acid (48%; 60 c.c.) were refluxed for 4 hours. The bulk of the acid was distilled off under reduced pressure, and the base liberated by aqueous ammonia and extracted with ether, dried (K_2CO_3), and distilled. An oil (15·7 g.), b. p. 112—113°/0·3 mm., was collected which slowly solidified when kept at 0° to a white mass, m. p. 44—45°. The *hydrochloride* crystallised from alcohol–ether in white crystals, m. p. 123° (Found: N, 6·7. $C_{11}H_{17}ON,HCl$ requires N, 6·5%). The *picrolonate* crystallised from alcohol in orange prisms, m. p. 191—192° (Found: N, 15·7. $C_{11}H_{17}ON,C_{10}H_8O_8N_4$ requires N, 15·8%). The base on hydrogenation in alcohol at 80°/80 atmospheres in presence of Raney nickel absorbed one molecular proportion of hydrogen. Diethylamine and *m*-cresol were isolated in 80% yield.

3-*Nitromethyl*cyclo*hexanone*.—To a stirred solution of nitromethane (9·4 g.) in methanol (20 c.c.) at 40° were added, at equivalent rates, a solution of sodium (3·75 g.) in methanol (50 c.c.) and of *cyclo*hex-2-enone (12 g.) (Whitmore and Pedlow, *J. Amer. Chem. Soc.*, 1941, **63**, 758) in methanol (10 c.c.). The mixture was stirred for 30 minutes, then cooled in ice water while acetic acid (50%; 25 c.c.) was added. Methanol was distilled off, the residue diluted with water and extracted with ether, and the extract washed with 2N-sodium carbonate, then with water, dried (K_2CO_3), and distilled. A viscous oil (10·4 g.), b. p. 100—102°/0·1 mm., was collected. The *semicarbazone* crystallised from alcohol in prisms, m. p. 167° (Found: C, 44·9; H, 6·9; N, 25·9. $C_8H_{14}O_3N_4$ requires C, 44·9; H, 6·6; N, 26·2%).

3-1′-*Nitroethyl*cyclo*hexanone*.—Prepared, as described for the previous compound, from nitroethane (46·4 g.) and *cyclo*hex-2-enone (48·5 g.), this was a viscous oil (65·5 g.), b. p. 101—102°/0·01 mm. The *semicarbazone* crystallised from alcohol in prisms, m. p. 179° (Found: N, 24·3. $C_9H_{16}O_3N_4$ requires N, 24·6%).

3-*Acetyl*cyclo*hexanone*.—3-1′-Nitroethyl*cyclo*hexanone (5·9 g.), dissolved in a solution of sodium hydroxide (1·6 g.) in water (30 c.c.), was added dropwise to sulphuric acid (30%; 35 c.c.) with stirring at 0°. Stirring was continued for 30 minutes while the solution attained room temperature. The solution was warmed slowly to 55°, saturated with ammonium sulphate, and extracted with ether (8 × 25 c.c.), and the extract dried (K_2CO_3) and distilled. An oil (3·15 g.), b. p. 140—145° (bath-temp.)/15 mm., was collected which solidified. 3-*Acetyl*cyclo*hexanone* crystallised from light petroleum (b. p. 60—80°) in plates, m. p. 39° (Found: C, 68·4; H, 8·6. $C_8H_{12}O_2$ requires C, 68·6; H, 8·6%). The *dioxime* crystallised from alcohol in prisms, m. p. 158° (Found: C, 56·4; H, 8·0; N, 16·1. $C_8H_{14}O_2N_2$ requires C, 56·5; H, 8·2; N, 16·5%).

Dehydrogenation. The ketone (3·15 g.) was heated with palladium black (0·2 g.) at 220—240° for 6 hours. Extraction with 2N-sodium hydroxide gave an alkali-soluble substance, b. p. 150—180° (bath-temp.)/16 mm., which, crystallised from benzene–light petroleum (b. p. 60—80°), had m. p. 90—93° (0·1 g.). The semicarbazone crystallised from alcohol in prisms, m. p. 194—195° alone or mixed with *m*-hydroxyacetophenone semicarbazone. Unchanged 3-acetyl*cyclo*hexanone (0·85 g.) was recovered.

3-1′-*Nitroethyl*cyclo*hexanol*.—3-1′-Nitroethyl*cyclo*hexanone (66·5 g.) was heated under reflux with aluminium *iso*propoxide (130 g.) in dry toluene (500 c.c.). Acetone ceased to be detectable in the refluxing toluene after 6 hours. The solution was then poured into 2N-hydrochloric acid, and the toluene layer separated, dried (K_2CO_3), and distilled. A viscous oil (46·3 g.), b. p. 108—115°/0·1 mm., was collected. The *phenylurethane*, on fractional crystallisation from benzene–light petroleum (b. p. 80—100°), gave two isomers, m. p. 115° (Found: N, 9·6. $C_{15}H_{20}O_4N_2$ requires N, 9·6%) and m. p. 86—87° (Found: N, 9·8%).

3-*Acetyl*cyclo*hexanol*.—3-1′-Nitroethyl*cyclo*hexanol (46·3 g.), by the method described for 3-acetyl-*cyclo*hexanone, gave 3-acetyl*cyclo*hexanol (30·4 g.), b. p. 134—138°/13 mm. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in yellow needles, m. p. 165° (Found: C, 52·0; H, 5·9; N, 17·3. $C_{14}H_{18}O_5N_4$ requires C, 52·2; H, 5·6; N, 17·4%). The *phenylurethane* crystallised from light petroleum (b. p. 80—100°) in needles, m. p. 91° (Found: N, 5·4. $C_{15}H_{19}O_3N$ requires N, 5·4%).

3-*Acetyl*cyclo*hexyl Bromide*.—3-Acetyl*cyclo*hexanol (1 g.) in hydrobromic acid (48%; 10 c.c.) was set aside at room temperature for 4 days. A heavy red oil slowly separated. The mixture was diluted with ice-water and extracted with ether, and the extract washed with sodium hydrogen carbonate solution, then with water, dried ($CaCl_2$), and distilled. An oil (1·05 g.), b. p. 130—135° (bath-temp.)/12 mm., was collected. The 2 : 4-dinitrophenylhydrazone was very soluble in all solvents except light petroleum and crystallised very slowly. The *semicarbazone* crystallised from alcohol in prisms, m. p. 180° (Found: N, 15·4; Br, 30·5. $C_9H_{16}ON_3Br$ requires N, 16·0; Br, 30·5%).

3-*Acetyl*cyclo*hexyl Iodide*.—Prepared as the bromide from 3-acetyl*cyclo*hexanol (10 g.) and hydriodic acid (100 c.c.), this was an oil (13·6 g.), b. p. 72—76°/0·03 mm. (decomp.), which gave a *semicarbazone*, prisms (from alcohol), m. p. 160° (Found: N, 14·1; I, 40·7. $C_9H_{16}ON_3I$ requires N, 13·6; I, 41·1%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in orange plates, m. p. 138—139° (Found: N, 13·0; I, 29·3. $C_{14}H_{17}O_4N_4I$ requires N, 13·0; I, 29·4%). Attempts to condense these halides with phenol or guaiacol in presence of alkalis led to tars and small yields of an oil with a powerful, pleasant odour, b. p. 95—100° (bath-temp.)/15 mm., which gave a 2 : 4-*dinitrophenylhydrazone*, brilliant red needles (from ethyl acetate), m. p. 203° (Found: C, 55·2; H, 5·4; N, 18·6. $C_{14}H_{16}O_4N_4$ requires C, 55·3; H, 5·2; N, 18·4%). The *semicarbazone* crystallised in plates (from alcohol), m. p. 206° (Found: N, 23·0. $C_9H_{15}ON_3$ requires N, 23·2%). The analyses are consistent with those required of 3-acetyl-*cyclo*hexene.

Dihydroresorcinol Mono-(o-methoxyphenyl) Ether.—3-Chlorocyclohex-2-enone (12 g.) (Crossley and Haas *J.*, 1903, **83**, 494) and guaiacol (12 g.) in acetone were refluxed with anhydrous potassium carbonate (15 g.) overnight, then filtered, and distilled. An oil, b. p. 210—230°/15 mm., which rapidly crystallised, was collected. The *ether* crystallised from benzene–light petroleum (b. p. 60—80°) in large prisms (14·1 g.), m. p. 97° (Found: C, 71·6; H, 6·5. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·4%).

Dihydroresorcinol Monophenyl Ether.—When prepared similarly from 3-chlorocyclohex-2-enone (22·6 g.) and phenol (16 g.), this *ether* formed an oil (28·9 g.), b. p. 194—196°/18 mm., which slowly solidified and crystallised from light petroleum (b. p. 60—80°) in plates, m. p. 39° (Found: C, 76·9; H, 6·8. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%).

Dihydroresorcinol o-Hydroxyphenyl Ether.—When prepared from 3-chlorocyclohex-2-enone (9·7 g.) and catechol (9·0 g.), the *o-hydroxyphenyl ether* (10·1 g.) had b. p. 170—185° (bath-temp.)/11 mm., rapidly solidified, and crystallised from benzene in pearly plates, m. p. 89—94° (decomp.) (Found: C, 70·4. H, 6·0. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%).

3-o-*Methoxyphenoxy*cyclo*hexanol.*—Dihydroresorcinol *o*-methoxyphenyl ether (twice distilled and twice crystallised) (7·5 g.) was shaken in ethyl acetate (100 c.c.) with hydrogen at room temperature and atmospheric pressure in presence of palladised charcoal (30%; 1 g.). 1100 C.c. of hydrogen were absorbed during 11 hours, whereafter the catalyst was changed to platinum oxide (0·3 g.). A further 780 c.c. of hydrogen were then absorbed during 8 hours. The solution was filtered and washed with 2N-sodium hydroxide to remove guaiacol. The ethyl acetate layer was dried and distilled. A viscous oil (5·5 g.), b. p. 189—198°/15 mm., was collected. The *phenylurethane* crystallised in needles (from alcohol), m. p. 121—122° (Found: C, 70·6; H, 6·4; N, 4·1. $C_{20}H_{23}O_4N$ requires C, 70·4; H, 6·7; N, 4·1%).

Reduction of Dihydroresorcinol Monophenyl Ether.—Reduction of this ether over palladised charcoal (30%) terminated with absorption of two molar proportions of hydrogen. The products were *cyclo*hexanone (identified as the semicarbazone, m. p. 166—167°) and phenol (identified as tribromophenol, m. p. 90—92°). The ether (14·6 g.) in alcohol (600 c.c.) was treated with sodium (20 g.) without cooling. The mixture was acidified at 5° with acetic acid and extracted with ether. The extract was dried (K_2CO_3) and distilled. A low-boiling fraction containing phenol and *cyclo*hexanol was rejected and the fraction (3·25 g.), b. p. 130—135° (bath-temp.)/20 mm., was collected. In attempts to prepare the phenylurethane, carbanilide (m. p. 238°) was isolated.

NN-*Diethyl*-4-*hydroxy*-3-*nitrobenzylamine.*—Diethylamine (24 g.) in dry benzene (40 c.c.) was added during 0·5 hour to a refluxing solution of 4-hydroxy-3-nitrobenzyl chloride (27·5 g.) (Fishman, *J. Amer. Chem. Soc.*, 1920, **42**, 2288) in benzene (40 c.c.), and refluxing was continued for 1 hour. The base was taken up in 2N-hydrochloric acid, precipitated by addition of potassium carbonate, and extracted with chloroform, dried (Na_2SO_4) and freed from solvent. The residue was dissolved in dry ether, and the *hydrochloride* (17·5 g.) precipitated by gaseous hydrogen chloride. It crystallised from alcohol in yellow prisms (15·8 g.), m. p. 185° (Found: N, 10·9. $C_{11}H_{16}O_3N_2$.HCl requires N, 10·8%). The *base* crystallised from alcohol in yellow prisms, m. p. 109° (Found: N, 12·5. $C_{11}H_{16}O_3N_2$ requires N, 12·5%). 4-*Acetoxy*-NN-*diethyl*-3-*nitrobenzylamine hydrochloride* crystallised from alcohol in white needles, m. p. 191° (Found: N, 9·3. $C_{13}H_{18}O_4N_2$.HCl requires N, 9·3%).

NN-*Diethyl*-4-*methoxy*-3-*nitrobenzylamine.*—(*a*) *NN*-Diethyl-4-hydroxy-3-nitrobenzylamine (2·4 g.) and trimethylphenylammonium hydroxide [from the toluene-*p*-sulphonate (3·3 g.) (Rodionov, *Bull. Soc. chim.*, 1926, **39**, 305)] in methanol (15 c.c.) were heated at 150° for 3 hours. The mixture was acidified with acetic acid and steam-distilled and the residue basified with 2N-sodium hydroxide. Ether extracted a small amount of oil which gave a hydrochloride, crystallising from alcohol–ether in small prisms, m. p. 216°, identical (mixed m. p.) with the product described below.

(*b*) 4-Methoxy-3-nitrobenzyl chloride (69·5 g.) (Jacobs and Heidelberger, *J. Biol. Chem.*, 1915, **20**, 676) and diethylamine (51 g.) were refluxed in absolute alcohol (500 c.c.) for 1 hour. The product was isolated in the same manner as *NN*-diethyl-4-hydroxy-3-nitrobenzylamine. The *hydrochloride* (58·3 g., 62%) crystallised from alcohol in needles, m. p. 218° Found: N, 10·2. $C_{12}H_{18}O_3N_2$.HCl requires N, 10·2%).

3-*Amino*-NN-*diethyl*-4-*methoxybenzylamine.*—Tin (32 g.) was added to a cold solution of *NN*-diethyl-4-methoxy-3-nitrobenzylamine hydrochloride (58·3 g.) in hydrochloric acid (*d* 1·16; 200 c.c.). The mixture became hot and a white solid separated which redissolved during 1 hour's heating on the steam-bath. The filtered solution was basified with 40% aqueous sodium hydroxide, and the precipitated oil was taken up in ether, dried (K_2CO_3), and distilled. The distillate (37 g.), b. p. 171—174°/16 mm., was converted into the *dihydrochloride*, m. p. 207° (from alcohol) (Found: N, 9·6. $C_{12}H_{20}ON_2$,2HCl requires N, 10·0%).

NN-*Diethyl*-3-*hydroxy*-4-*methoxybenzylamine.*—3-Amino-4-methoxybenzyldiethylamine (4 g.) in sulphuric acid (50%; 10 c.c.) was diazotised at 0° by sodium nitrite solution (10%; 17·5 c.c.), and the solution added dropwise to a boiling (105°) solution of copper sulphate (35 g.) in water (35 c.c.). Boiling was continued for 3 minutes after the completed addition. The cooled solution was filtered, basified with aqueous ammonia, and extracted with chloroform, and the extract dried (K_2CO_3) and distilled. The distillate, b. p. 160° (bath-temp.)/13 mm., crystallised from light petroleum (b. p. 60—80°), giving the *hydroxy-amine* as prisms (0·3 g., 7%), m. p. 76° (Found: C, 68·6; H, 9·0; N, 6·9. $C_{12}H_{19}O_2N$ requires C, 68·9; H, 9·1; N, 6·7%). In a similar experiment, which could not be repeated, the yield was 0·9 g. (22%). Other methods gave negative results.

3-*Bromo*-NN-*diethyl*-4-*methoxybenzylamine.*—The diazonium solution from 3-amino-*NN*-diethyl-4-methoxybenzylamine (18·5 g.) in hydrobromic acid (24%; 50 c.c.) was added to a freshly prepared cuprous bromide mixture prepared from copper sulphate (6 g.) at 0°. The mixture was warmed slowly to 80°,

then basified with aqueous ammonia, and the solution extracted with chloroform. The extract was dried (K_2CO_3) and distilled, to give a pale yellow oil (9·6 g.), b. p. 170—175°(bath temp.)/15 mm. The *hydrochloride* crystallised from alcohol–ether in hard prisms, m. p. 195° (Found: N, 4·7; Cl, 11·6. $C_{13}H_{18}ONBr,HCl$ requires N, 4·5; Cl, 11·5%).

(±)-3-*Hydroxy-4-methoxy-α-methylbenzylamine.*—*iso*Acetovanillone oxime (3 g.) (Schneider and Kraft, *Ber.*, 1922, **55**, 1896) in aqueous methanol (50%; 70 c.c.) was reduced by addition of sodium amalgam (3%; 100 g.) in small portions. The mixture was kept faintly acid by addition of acetic acid (50%). The solution was decanted from mercury, 5N-hydrochloric acid (5 c.c.) added, and unchanged oxime shaken out with ether. The product was precipitated by potassium carbonate and extracted with ether, the extract dried (K_2CO_3), and the ether distilled off. The residue, on crystallisation from benzene (charcoal), gave (±)-3-*hydroxy-4-methoxy-α-methylbenzylamine* as prisms (1·9 g.), m. p. 148° (Found: N, 8·3. $C_9H_{13}O_2N$ requires N, 8·4%).

3-cyclo*Hexyloxy-4-methoxyacetophenone.*—*iso*Acetovanillone (90 g.) (Coulthard, Marshall, and Pyman, *J.*, 1930, 290) and *cyclo*hexyl bromide (600 g., 6 mols.) were heated under reflux in alcohol (2 l.) while a solution of sodium hydroxide (146 g.) in methanol (600 c.c.) was added during 80 hours. Refluxing was continued for 8 hours more. The mixture was cooled to 0°, filtered from sodium bromide, and evaporated to small bulk. The residue was treated with 2N-sodium hydroxide, and the insoluble oil extracted with ether, dried (K_2CO_3), and distilled. A viscous oil (56·8 g.), b. p. 195—200°/10 mm., was collected which soon solidified. 3-cyclo*Hexyloxy-4-methoxyacetophenone* (53·5 g.) crystallised from 70% alcohol in large prisms, m. p. 61° (Found: C, 72·6; H, 8·1. $C_{15}H_{22}O_3$ requires C, 72·6; H, 8·1%). Unchanged *iso*acetovanillone (30·5 g.) was recovered. The 2:4-*dinitrophenylhydrazone* crystallised from acetic acid in red needles, m. p. 191° (Found: N, 13·3. $C_{21}H_{24}O_6N_4$ requires N, 13·1%). The *oxime* crystallised from alcohol in needles, m. p. 99° (Found: N, 5·4. $C_{15}H_{21}O_3N$ requires N, 5·3%).

(±)-3-cyclo*Hexyloxy-4-methoxy-α-methylbenzylamine.*—3-*cyclo*Hexyloxy-4-methoxyacetophenone oxime (6·7 g.) was reduced as described for (±)-3-hydroxy-4-methoxy-α-methylbenzylamine. The base was an oil, b. p. 210—215°/13 mm., which solidified when kept below 10° but melted at 15—20°. The *hydrochloride* (5·2 g.) crystallised from alcohol–ether in needles, m. p. 213° (Found: N, 4·9; Cl, 12·3. $C_{15}H_{23}O_2N,HCl$ requires N, 4·9; Cl, 12·4%).

(±)-3-cyclo*Hexyloxy-4-methoxy-α-methylbenzyl Alcohol.*—3-*cyclo*Hexyloxy-4-methoxyacetophenone (16·0 g.) in ethyl acetate (50 c.c.) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of platinum oxide (0·2 g.). Further additions of catalyst were required at 14% and 54% reduction, and reduction was terminated after 35 hours at 85% of the theoretical absorption of hydrogen. The solution was filtered and distilled. A thick colourless oil (13 g.), b. p. 210—220°/17 mm., was collected. The *phenylurethane* crystallised from light petroleum in needles, m. p. 163° (decomp.) (Found: C, 71·8; H, 7·4; N, 3·9. $C_{22}H_{27}O_4N$ requires C, 71·5; H, 7·3; N, 3·8%).

(±)-NN-*Dialkyl*-3-cyclo*hexyloxy-4-methoxy-α-methylbenzylamines.*—3-*cyclo*Hexyloxy-4-methoxy-α-methylbenzyl alcohol was converted into the bromide by addition of phosphorus tribromide (0·33 mol.) at <10° to its solution in dry benzene. After 1 hour at room temperature the mixture was treated with ice, and the benzene layer separated, washed with sodium hydrogen carbonate solution, and dried (Na_2SO_4). The appropriate dialkylamine was added and the mixture set aside overnight, then refluxed for 1 hour. Dialkylamine hydrobromide was filtered off, the benzene layer evaporated, and the residue dissolved in ether. Amines were extracted by repeated shaking with small quantities of 10% hydrochloric acid, and the base regenerated with ammonia, taken up in ether, dried, and distilled. The hydrochlorides were crystallised from alcohol–ether. The *products* are recorded in the table.

(±)-NN-*Dialkyl*-3-cyclo*hexyloxy-4-methoxy-α-methylbenzylamines.*

NR_2	B. p. of base (bath-temp.)	Hydrochloride, m. p.	Formula	Found, %			Required, %		
				C	H	N	C	H	N
NMe_2	145—150°/0·5 mm.	191°	$C_{17}H_{27}O_2N,HCl$	65·0	8·7	4·6	65·1	8·9	4·5
NEt_2	135—145°/0·03 mm.	110	$C_{19}H_{31}O_2N,HCl$	66·1	9·2	4·0	66·8	9·4	4·1
NPr^n_2	150—160°/0·1 mm.	135	$C_{21}H_{35}O_2N,HCl$	68·0	9·6	4·2	68·2	9·7	3·8
NBu^n_2	160—165°/0·5 mm.	133	$C_{23}H_{39}O_2N,HCl$	—	—	3·7†	—	—	3·5
Tiq *	180—190°/0·05 mm.	179	$C_{24}H_{31}O_2N,HCl$	71·8	8·1	3·5	71·7	8·0	3·5

* Tetrahydro*iso*quinolino. † Found: Cl, 9·2. Required: Cl, 8·9%.

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Department of Biochemistry, Institute of Psychiatry, Denmark Hill, London, S.E.5.

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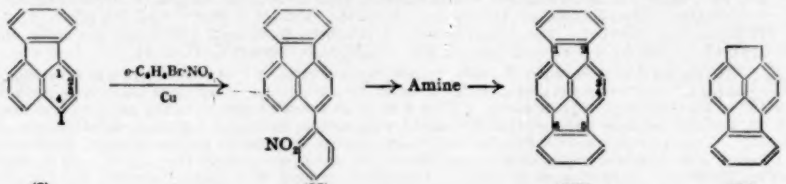
651. *Synthesis of Fluoranthenes. Part VII.** 1 : 2-5 : 6-*Dibenzopyracylene.*

By H. W. D. Stubbs and S. Horwood Tucker.

1 : 2-5 : 6-Dibenzopyracylene (III) has been unambiguously synthesised by a crossed Ullmann reaction from 4-iodofluoranthene and *o*-bromonitrobenzene, followed by the usual method of cyclisation. Attempts to obtain (III) by cyclisation of 4-phenylfluoranthene, and from 2-9′-fluorenylethyl *o*-nitrophenyl ketone (VI), prepared by a Mannich reaction, failed.

Very little work has been done on the ultra-violet absorption spectra of fluoranthene derivatives (Seshan, *Proc. Indian Acad. Sci.*, 1936, **43**, 148; Orchin and Reggel, *J. Amer. Chem. Soc.*, 1947, **69**, 505; 1951, **73**, 436; Kloetzel and Chubb, *ibid.*, 1950, **72**, 150; Deno, *ibid.*, p. 4057). 1 : 2-5 : 6-Dibenzopyracylene † (III) has now been examined (Clar, Stubbs, and Tucker, *Nature*, 1950, **166**, 1075) with particular reference to Clar's anellation theory (Clar, *J. Chem. Physics*, 1949, **17**, 741; *Chem. Ber.*, 1949, **82**, 495; "Aromatische Kohlenwasserstoffe," Berlin, Springer, 1941, p. 20): it has been shown that *p*-absorption in 1 : 2-5 : 6-dibenzopyracylene and in fluoranthene is located in the naphthalene ring system present in these hydrocarbons. The spectra of (III) and of 4-phenylfluoranthene are now compared (see figure). The examination of other fluoranthene derivatives is proceeding.

Synthesis of 1 : 2-5 : 6-dibenzopyracylene was readily accomplished by the established method of synthesis of fluoranthene and its derivatives (Forrest and Tucker, *J.*, 1948, 1137; Tucker and Whalley, *J.*, 1949, 632, 3215; Hawkins and Tucker, *J.*, 1950, 3286): 4-iodofluoranthene (I) by a crossed Ullmann reaction with *o*-bromonitrobenzene, by means of copper, gave 4-*o*-nitrophenylfluoranthene (II), catalytically reduced to the corresponding amine,



(I) (II) (III) (IV)

which on diazotisation and treatment of the diazonium solution with copper bronze gave 1 : 2-5 : 6-dibenzopyracylene (III), bright orange needles, m. p. 261—262°. The iodine atom in (I) is definitely in the 4-position since (I) was prepared from 4-nitrofluoranthene (von Braun and Manz, *Annalen*, 1931, **488**, 111) by the usual reduction–diazotisation–Sandmeyer route. All attempts to iodinate fluoranthene directly failed to give pure 4-iodofluoranthene. 4-Iodofluoranthene was chosen in preference to the corresponding bromo-compound on account of the low reactivity of the latter; *e.g.*, 4-bromofluoranthene needs to be heated to 300° with copper to give 4 : 4′-difluoranthyl (*idem*, *Ber.*, 1937, **70**, 1607).

The ease of cyclisation in the last stage of the synthesis of (III) is in striking contrast to the unsuccessful attempts of others to prepare ace-acenaphthene derivatives (see Fieser and Peters, *J. Amer. Chem. Soc.*, 1932, **54**, 4347; Mayer and Kaufmann, *Ber.*, 1920, **53**, 289; Fleischer and Wolff, *ibid.*, p. 925). On the other hand, Kloetzel and Chubb (*loc. cit.*) have prepared 4 : 5-dimethylenefluoranthene (5 : 6-dihydro-1 : 2-benzopyracylene) (IV) from 1 : 2 : 3 : 4- tetrahydro-4-ketofluoranthene. The structure of (IV) was supported by the similarity of its ultra-violet absorption spectrum to that of fluoranthene.

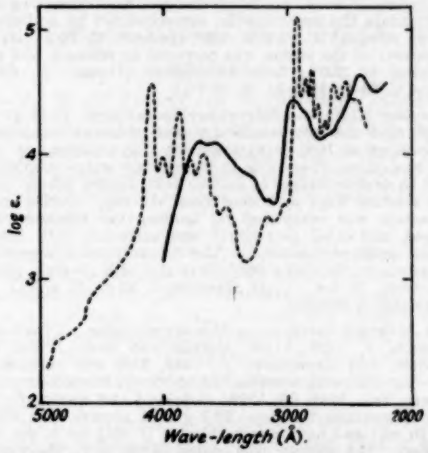
The facile cyclisations of diphenyl- and of dichlorodiphenyl-tetracenes to give 5 : 6-11 : 12-diphenylenetetracene (Badoche, *Ann. Chim.*, 1933, **20**, 200; Dufraisse and Girard, *Bull. Soc. chim.*, 1934, **1**, 1359; Dufraisse, *ibid.*, 1936, **3**, 1857; Dufraisse and Horclois, *ibid.*, p. 1894) bear a resemblance to that now reported by us since all involve formation of a *peri*-phenylene grouping. We found that formation of the second five-membered ring in the final stage of

* Part VI, *J.*, 1950, 3288.

† For the name "pyracylene" see *J.*, 1951, 2391.

synthesis of (III) was as easy as that of the five-membered ring of fluoranthene, the method of cyclisation being the same in the two cases.

An attempt to synthesise (III) by utilization of the Mannich reaction (Stubbs and Tucker, *J.*, 1950, 3288) failed; although methyl fluorene-9-carboxylate readily condensed with 2-diethylaminoethyl *o*-nitrophenyl ketone, in the usual manner, to give 2-(9-carbomethoxy-9-fluorenyl)ethyl *o*-nitrophenyl ketone (V), smoothly hydrolysed with loss of carbon dioxide to 2-9′-fluorenylethyl *o*-nitrophenyl ketone (VI). This ketone, however, could not be reduced to the alcohol by the aluminium *iso*propoxide method although excellent results were obtained with the un-nitrated 2-9′-fluorenylethyl phenyl ketone (Stubbs and Tucker, *loc. cit.*), and with



Absorption spectra of 1 : 2-5 : 6-*dibenzopyracylene* (– – – –) *and of* 4-*phenylfluoranthene* (——) *in ethanol. Band maxima* (*in* Å), 1 : 2-5 : 6-*dibenzopyracylene*: p-*bands* 4100, 4020, 3870, 3795, 3670, 3490; β-*bands* 2925, 2865, 2810, 2760, 2705; β′-*bands* 2625, 2530. 4-*Phenylfluoranthene*: p-*bands* 3700, 3580, 3145; β-*band* 2940; β′-*band* 2405.

phenyl 2-9′-fluorenyl-2-phenylethyl ketone (Tucker and Whalley, *J.*, 1949, 50). Attempts to cyclise both (V) and (VI) by hydrogen bromide failed (cf. France, Tucker, and Forrest, *J.*, 1945, 7).

Heating of 4-phenylfluoranthene at 110—140° with a mixture of anhydrous aluminium chloride and sodium chloride failed to give 1 : 2-5 : 6-dibenzopyracylene.

Experimental.

4-Iodofluoranthene (I).—4-Nitrofluoranthene (8 g.), suspended in glacial acetic acid (150 ml.) with 10% palladium–charcoal catalyst (0·8 g.) added, was reduced by hydrogen (theoretical volume absorbed in 3—4 hours) to give a green fluorescent solution. After filtration, the catalyst was extracted several times with boiling glacial acetic acid, the combined filtrates were diluted with water (150 ml.), concentrated sulphuric acid (10 ml.) was added, and the solution diazotised at −5° to 0° by addition of sodium nitrite (2·5 g.) in water. After destruction of excess of nitrite with urea (1 g.), the solution was poured into a solution of potassium iodide (30 g.) in water (150 ml.) and kept at room temperature overnight. After filtration, thorough washing, and drying, the residue was extracted by light petroleum (b. p. 60—80°). After the usual treatment (thiosulphate–charcoal) and finally crystallisation from ethanol, cream-coloured micro-leaflets of *4-iodofluoranthene*, m. p. 109—110° (2·95 g., 28%) (Found: C, 58·6; H, 2·9; I, 38·55. $C_{16}H_9I$ requires C, 58·6; H, 2·8; I, 38·7%), were obtained.

4-o-Nitrophenylfluoranthene (II).—4-Iodofluoranthene (1 g.) and *o*-bromonitrobenzene (0·65 g.) were heated to 210—220°, and copper bronze (0·5 g.; washed with carbon tetrachloride) was added in

portions during 2 hours, with frequent stirring. Heating was continued for a further 2 hours, the cooled mass extracted with acetone, and the residue obtained on evaporation of the acetone was dissolved in light petroleum (b. p. 60—80°) and chromatographed (alumina). Benzene–light petroleum (1 : 1, v/v) gave a yellow eluate with a green fluorescence from which a yellow solid, crystallising from ethanol, was obtained (0·85 g., 83%). Recrystallisation, with loss of material, by dissolution in ethyl acetate and then addition of an equal volume of methanol gave lemon-yellow needles, m. p. 157—160° (softening at 155°), of *4-o-nitrophenylfluoranthene* (Found: C, 81·3; H, 4·1. $C_{22}H_{13}O_2N$ requires C, 81·7; H, 4·05%). The use of three times the above amount of *o*-bromonitrobenzene facilitated mixing and gave similar results but removal of excess was troublesome, as also was removal of *oo'*-dinitrodiphenyl formed.

4-o-Aminophenylfluoranthene.—Reduction of the nitro-compound (II) was accomplished by hydrogen with either (*a*) 10% palladium–charcoal and glacial acetic acid or (*b*) Raney nickel and ethanol. Since the isolated amine, a pale brown oil, could not be crystallised, it was dissolved in ether, and dry hydrogen chloride passed in to precipitate the *hydrochloride*, reprecipitated by addition of ether to the ethanol solution, to give pale green needles, m. p. 210—250° (Found: C, 79·3; H, 4·8. $C_{22}H_{16}NCl$ requires C, 80·1; H, 4·9%). A *picrate* of the amine was prepared in ethanol, and gave golden-brown cubes, m. p. 217—219° (softening at 200°), from chloroform (Found: C, 64·4; H, 3·6; N, 10·6. $C_{22}H_{15}N,C_6H_3O_7N_3$ requires C, 64·4; H, 3·5; N, 10·7%).

1 : 2-5 : 6-*Dibenzopyracylene* (III).—4-*o*-Nitrophenylfluoranthene (0·46 g.) was reduced (hydrogen, Raney nickel, and ethanol), and the uncrystallised amine obtained was dissolved in acetic acid and poured with stirring into excess of 10% (v/v) sulphuric acid solution. A solution of sodium nitrite (0·12 g.) in water (3 ml.) was added all at once to the slightly warm solution; after diazotisation was complete, urea was added to destroy excess of nitrous acid, copper bronze (washed with carbon tetrachloride) added, and the mixture kept with occasional stirring. During *ca.* 1 hour an orange solid gradually separated: reaction was completed by heating the mixture on the steam-bath for ½ hour. The filtered, washed, and dried precipitate was extracted with benzene, and the red-green fluorescing solution chromatographed (alumina). The concentrated orange eluate gave orange needles of 1 : 2-5 : 6-*dibenzopyracylene*, m. p. 261—262° (0·15 g., 38% overall yield from 4-*o*-nitrophenylfluoranthene) (Found: C, 95·6; H, 4·4. $C_{22}H_{12}$ requires C, 95·6; H, 4·4%). Picric acid and 2 : 4 : 7-trinitrofluorenone gave unstable complexes.

Attempted Synthesis by Mannich Reaction.—*o-Nitroacetophenone.* Direct nitration of acetophenone (Elson, Gibson, and Johnson, *J.*, 1930, 1128; Morgan and Moss, *J. Soc. Chem. Ind.*, 1923, 461T; Simpson, Atkinson, Schofield, and Stephenson, *J.*, 1945, 646) was unsuitable owing to difficulty of removal of the *m*-isomer. The following modification of the synthesis from *o*-nitrobenzoic acid (Walker and Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 1386; Schofield and Swain, *J.*, 1948, 384; Bowman, *J.*, 1950, 324) was adopted: Magnesium turnings (10·7 g., 1·1 atoms) were allowed to react vigorously with anhydrous ethanol (10 ml.) and carbon tetrachloride (1 ml.) for a few minutes, then anhydrous benzene (150 ml.) was added. The mixture was heated to the b. p., the source of heat removed, and the contents of the flask stirred vigorously while a mixture of ethyl malonate (70·4 g., 1·1 mols.), anhydrous ethanol (40 ml.), and anhydrous benzene (50 ml.) was added at such a rate that vigorous refluxing was maintained, with heating if necessary. The mixture was stirred under reflux till all the magnesium was in solution (*ca.* 30 minutes), the source of heat removed, and vigorous stirring maintained while *o*-nitrobenzoyl chloride (74·2 g., 1 mol.) in anhydrous benzene (100 ml.) was added as rapidly as the violence of the reaction would allow. After being boiled (30 minutes), the mixture was cooled slightly, and dilute sulphuric acid added cautiously with stirring. The mixture at first became very pasty, but further addition of acid gave two clear layers. The whole was then submitted to distillation till the temperature of the vapour reached 95°, a mixture of acetic acid (120 ml.), concentrated sulphuric acid (15 ml.), and water (80 ml.) was added, and the mixture boiled (4 hours). It was cooled (ice–salt), made strongly alkaline with solid potassium hydroxide, and shaken with ether, the whole was filtered, and the residue washed well with ether. The organic layer of the filtrate was separated, washed with water, dried, and distilled. The fraction of b. p. 158·5—159°/16 mm. (166·5°/21 mm.) was pure *o*-nitroacetophenone (58·2 g., 88%). [*o*-Nitrobenzoyl chloride was prepared as required by boiling the acid (67 g.) with thionyl chloride (100 ml.) till all was in solution. Excess of thionyl choride was removed under reduced pressure, last traces being removed by addition and distillation of benzene (50 ml., 3 times). The acid chloride was used without further purification, as distillation under reduced pressure led to explosive decomposition.]

2-(9-Carbomethoxy-9-fluorenyl)ethyl o-nitrophenyl ketone (V). 2-Diethylaminoethyl *o*-nitrophenyl ketone hydrochloride (3·6 g., 1·5 mols.) (Mannich and Dannehl, *Arch. Pharm.*, 1938, **276**, 206) was dissolved in dry methanol (7 ml.), and a solution of sodium (0·3 g., 1·5 atoms) in methanol (3 ml.) added; after a few minutes' stirring, sodium chloride was filtered off, washed with a little methanol, and the combined filtrates were mixed with methyl iodide (1·6 g., 1·3 mols.) and added to a warm solution of methyl fluorene-9-carboxylate (2·4 g., 1·3 mols.) and sodium (0·24 g., 1·3 mols.) in methanol (10 ml.). Crystals appeared immediately and, on cooling, practically pure *2-(9-carbomethoxy-9-fluorenyl)ethyl o-nitrophenyl ketone* (V) (3 g., 71%) was deposited. Crystallisation from methyl cyanide gave needles, m. p. 168—169° (Found: C, 71·6; H, 4·95; N, 3·5. $C_{24}H_{19}O_5N$ requires C, 71·8; H, 4·8; N, 3·5%).

2-9'-Fluorenylethyl o-nitrophenyl ketone (VI). The ketone (V) (3 g.) was boiled (1 hour) with a mixture of acetic acid (90 ml.), concentrated sulphuric acid (6 ml.), and water (30 ml.), and poured into water (300 ml.); the resulting acid was filtered off and washed with water, but it was decarboxylated too readily for purification. It was boiled (15 minutes) in methyl cyanide (30 ml.), and the mixture diluted at the b. p. till crystallisation commenced; on cooling, *2-9'-fluorenylethyl o-nitrophenyl ketone* (VI) (1·7 g., 66%) was obtained. Crystallisation from ethanol or methyl cyanide gave needles, m. p. 147—149° (Found: C, 77·2; H, 4·8; N, 4·1. $C_{23}H_{17}O_3N$ requires C, 77·0; H, 5·0; N, 4·1%).

The acid was also decarboxylated by heating it at 170—180° till evolution of carbon dioxide ceased (21%). Attempted hydrolysis of (V) by aqueous-alcoholic sodium hydroxide gave a tarry product.

The ketone (VI) could not be induced to give an oxime (cf. Von Auwers, Lechner, and Bundesmann, *Ber.*, 1925, **58**, 50, who prepared an oxime of *o*-nitroacetophenone).

Reduction of (VI) by hydrogen and Raney nickel in ethyl acetate gave theoretical absorption of hydrogen for reduction of the nitro-ketone to the carbinol-amine compound, but neither could this nor its picrate be isolated, and ring closure to (III) could not be effected.

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UNIVERSITY OF GLASGOW. [*Received, May 10th*, 1951.]

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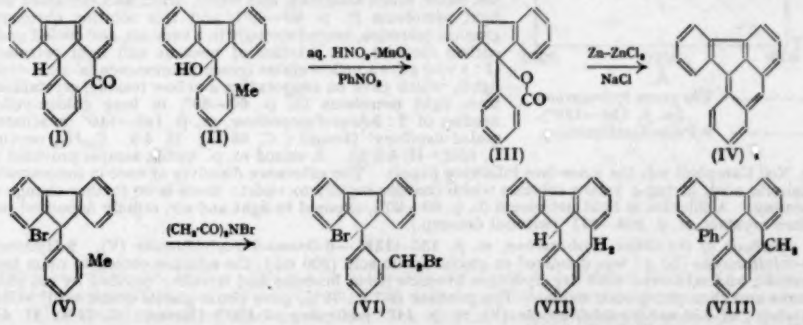
652. *Synthesis of Fluoranthenes. Part VIII.** 2 : 3-*Benzofluoranthene.*

By H. W. D. STUBBS and S. HORWOOD TUCKER.

2 : 3-Benzofluoranthene has been synthesised from *o*-diphenylenephthalide (III) by Clar's zinc-dust reduction method. An attempt to prepare the hydrocarbon from 9-bromo-9-(ω-bromo-*o*-tolyl)fluorene (VI) by the action of aluminium chloride in benzene gave chiefly a green hydrocarbon which may be 1 : 9-diphenylanthracene.

ALTHOUGH Weiss and Knapp [*Sitz. Wien. Akad., Kl.* II B (*Chemie*), 1932, **141**, 432] synthesised 1 : 9-phenylene-10-anthrone (1 : 4-dihydro-4-keto-2 : 3-benzofluoranthene) (I), they did not convert it into 2 : 3-benzofluoranthene (IV). We have synthesised (IV) from 9-hydroxy-9-*o*-tolylfluorene (II) (Weiss and Knapp, *loc. cit.*; Adams and Campbell, *J. Amer. Chem. Soc.*, 1950, **72**, 154) by oxidation to *o*-diphenylenephthalide (III), which was converted by the zinc-dust reduction method (Clar, *Ber.*, 1939, **72**, 1645) into 2 : 3-benzofluoranthene (IV).

Another attempt to synthesise 2 : 3-benzofluoranthene was made by treatment of the alcohol (II) with hydrobromic acid in glacial acetic acid, to give 9-bromo-9-*o*-tolylfluorene (V), which, by bromination with *N*-bromosuccinimide gave 9-bromo-9-(ω-bromo-*o*-tolyl)fluorene (VI). Aluminium chloride in boiling benzene reacted with (VI) to give a small amount of what was probably (IV); but the greater part was a pale green, strongly-fluorescent hydrocarbon, m. p. 135—138°, whose analytical results for carbon and hydrogen agree closely with those required for dihydrobenzofluoranthene, or, phenyl- or diphenyl-anthracene; but molecular-weight determinations indicated diphenylanthracene. Formation of an anthracene derivative is understandable if, after cyclisation involving the bromomethyl group and the 1-position of the fluorene skeleton, fission of the 5-membered ring occurs. The green hydrocarbon cannot be 1-phenylanthracene (m. p. 110°); and 9-phenylanthracene (synthesised as by Krollpfeiffer and Branscheid, *Ber.*, 1923, **56**, 1617) is excluded both by its melting point (155—157°) and by its different ultra-violet absorption (see figure).



Absorption maxima (in Å) of the green hydrocarbon, of 9-phenylanthracene, and of anthracene are compared in the Table. It will be seen that with the green hydrocarbon there

* Part VII, preceding paper.

is a bathochromic shift of the main absorption bands, relative to 9-phenylanthracene; this is approximately what would be expected for addition of one aryl substituent to 9-phenylanthracene.

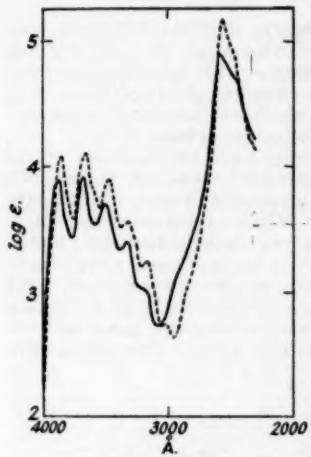
Green hydrocarbon (m. p. 135—138°)	3870	3670	3490	3320	3170	2580
9-Phenylanthracene	3840	3645	3465	3305	3160	2555
Anthracene	3745	3545	3380	3230	3080	2515

Formation of 1 : 9-diphenylanthracene could arise from reaction of the solvent, benzene, with the 9-bromine atom in (VI), to give 9-phenyl-9-(ω-bromo-*o*-tolyl)fluorene (VI; Ph instead of 9-Br); this then, by cyclisation, would give 1 : 4-dihydro-1-phenyl-2 : 3-benzofluoranthene (VIII), which, owing to molecular overcrowding round the 9-carbon atom of the fluorene nucleus, might rearrange to form 1 : 9-diphenylanthracene. The green hydrocarbon cannot be (VIII) since a compound of this formula would have a spectrum resembling that of fluorene and not of anthracene.

An attempt to prepare 1 : 4-dihydro-2 : 3-benzofluoranthene by reduction of *o*-diphenylenephthalide (III) failed.

Experimental.

o-Diphenylenephthalide (III).—9-Hydroxy-9-*o*-tolylfluorene (II) (10 g.), manganese dioxide (0·25 g.), concentrated nitric acid (170 ml.), water (340 ml.), and enough nitrobenzene to render the organic layer readily mobile were boiled together for 70 hours. The nitrobenzene was removed by steam-distillation, and the residue cooled, filtered, and dissolved in alcoholic sodium hydroxide. After dilution with four times its volume of water, and filtration, the filtrate was acidified. The precipitate was filtered off, washed, and dried, giving the phthalide (III) (5·5 g., 53%), m. p. 216—220°. Crystallisation from acetic acid raised the m. p. to 226°, with considerable loss of material (cf. Koelsch, *J. Amer. Chem. Soc.*, **1933**, **55**, 3394, who gives 219—220°). The use of vanadium pentoxide (Rieve and Myers, *J. Amer. Chem. Soc.*, 1951, **73**, 1371) in place of manganese dioxide was of no advantage. Heating at 210° for 9 hours with 30% nitric acid alone gave a low-melting compound, apparently with breakdown of the molecule. Potassium permanganate in acetone had no effect on (II) (cf. Weiss and Knapp, *loc. cit.*); chromium trioxide in glacial acetic acid gave fluorenone (cf. Koelsch, *J. Amer. Chem. Soc.*, 1932, **54**, 3389; 1933, *loc. cit.*).



——— *The green hydrocarbon (m. p. 135—138°).*
– – – – – 9-*Phenylanthracene.*

2 : 3-*Benzofluoranthene*.—The phthalide (III) (3 g.) and pure zinc dust (6 g.) were ground together very thoroughly and mixed with powdered sodium chloride (6 g.). To this were added powdered zinc chloride (30 g.) and ten drops of water, and the temperature raised to 270° with vigorous stirring. During 8 minutes the temperature was allowed to rise to 340°, with stirring, the mass was cooled, decomposed with boiling water and a little acetic acid, and filtered, the residue washed well with, successively, hot water, dilute ammonia, and water, dried, and extracted with light petroleum (b. p. 60—80°), and this solution chromatographed (alumina, heated strongly in a vacuum, and cooled under carbon dioxide). A mixture of benzene and light petroleum (1 : 1 v/v) gave a yellow eluate (green fluorescence in ultra-violet light), which gave on evaporation a yellow residue, crystallising from light petroleum (b. p. 60—80°) in long golden-yellow needles of 2 : 3-*benzofluoranthene*, m. p. 145—146° (evacuated, sealed capillary) (Found: C, 95·15; H, 4·9. $C_{20}H_{12}$ requires C, 95·2; H, 4·8%). A mixed m. p. with a sample provided by Dr. Neil Campbell was the same (see following paper). The substance dissolves at once in concentrated sulphuric acid, giving a yellow solution which changes rapidly to violet; there is no further change on warming. A solution in light petroleum (b. p. 60—80°), exposed to light and air, rapidly deposited pale yellow crystals, m. p. 208—211° (without decomp.).

Synthesis of the Green Hydrocarbon, m. p. 135—138°.—*9-Bromo-9-o-tolylfluorene* (V). 9-Hydroxy-9-*o*-tolylfluorene (10 g.) was dissolved in glacial acetic acid (200 ml.), the solution cooled to room temperature, and saturated with dry hydrogen bromide (from bromine and tetralin; purified by red phosphorus and then phosphoric oxide). The product (9·7 g., 79%) gave (from glacial acetic acid) yellow platelets of *9-bromo-9-o-tolylfluorene* (V), m. p. 142° (softening at 120°) (Found: C, 71·8; H, 4·4. $C_{20}H_{15}Br$ requires C, 71·7; H, 4·5%).

9-Bromo-9-(ω-bromo-o-tolyl)fluorene (VI). 9-Bromo-9-*o*-tolylfluorene (V) (1 g., 1·05 mols.) was dissolved in carbon tetrachloride (10 ml.), *N*-bromosuccinimide (0·5 g., 1 mol.) and benzoyl peroxide (trace) were added, and the mixture was boiled (irradiation by light) till all the *N*-bromosuccinimide had reacted (several hours). After filtration whilst hot, and extraction of the succinimide residue with boiling carbon tetrachloride, the combined filtrates were evaporated and the residue was crystallised from acetic acid (crude yield, 1 g., 86%). Recrystallisation from methyl cyanide or acetic acid slowly raised the m. p. to 158—161° (softening at 140°), giving yellow prisms of, essentially, 9-bromo-9-(ω-

bromo-*o*-tolyl)fluorene (VI), contaminated with a little more-highly brominated impurity (Found: C, 54·1; H, 3·45. Calc. for $C_{33}H_{14}Br_2$: C, 58·0; H, 3·4%).

Attempted cyclisation of (VI). The compound (VI) (2 g.) was dissolved in dry benzene (50 ml.), and finely-powdered aluminium chloride (10 g.) was added. A purple complex formed, and the mixture was boiled until evolution of hydrogen halide ceased (20 minutes). After decomposition of the complex in the usual way, the benzene solution was evaporated, and the residue dissolved in light petroleum (b. p. 60—80°) and chromatographed (alumina). The first colourless eluate (blue fluorescence in ultra-violet light) gave, on evaporation, a residue which crystallised from ethanol in pale green needles (0·3 g.), m. p. 135—138° [Found: C, 94·3; H, 5·5%; *M*, (Rast, camphor) 311, 313, (ebullioscopic, benzene) 341. Calc. for $C_{16}H_{14}$: C, 94·45; H, 5·55%; *M*, 254. Calc. for $C_{18}H_{12}$: C, 94·5; H, 5·5%; *M*, 330]. Further treatment of the column with a mixture of light petroleum and benzene (1 : 1 v/v) gave a yellow eluate with a green fluorescence, probably a very small quantity of 2 : 3-benzofluoranthene.

Reduction of o-*Diphenylenephthalide* (III) *with Hydriodic Acid and Phosphorus.*—The phthalide (III) (1·9 g.), constant-boiling hydriodic acid (50 ml.), red phosphorus (7 g.), and xylene (20 ml.) were boiled for 72 hours. After filtration, the residue was extracted well with hot dilute sodium hydroxide solution, and the organic layer of the filtrate washed with water and then dilute sodium hydroxide solution. The combined alkaline solutions gave, on acidification, 9-*o*-carboxyphenylfluorene (Weiss and Knapp, *loc. cit.*; Koelsch, *loc. cit.*). The residue from evaporation of the organic layer gave, on chromatography in the usual manner, a very small amount of 2 : 3-benzofluoranthene.

We are grateful to the Department of Scientific and Industrial Research for a grant (to H. W. D. S.), to Dr. E. Clar for the ultra-violet absorption curves, and to Mr. J. M. L. Cameron and Miss R. H. Kennaway of this Department for microanalyses.

UNIVERSITY OF GLASGOW. [*Received, July 9th,* 1951.]

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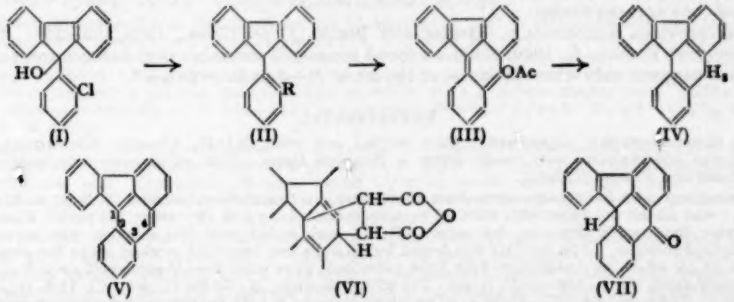
653. *Synthesis of* 2 : 3-*Benzofluoranthene.*

By NEIL CAMPBELL and ANGUS MARKS.

Two syntheses of 2 : 3-benzofluoranthene are described.

THE only simple 2 : 3-benzofluoranthene derivative described in the literature is 1 : 9-phenylene-10-anthrone (1 : 4-dihydro-4-keto-2 : 3-benzofluoranthene) (VII) described by Weiss and Knapp (*Monatsh.*, 1932, **61**, 61). We have now synthesised 2 : 3-benzofluoranthene (V) and find it to be identical with the hydrocarbon synthesised by Stubbs and Tucker (see preceding paper). Fluorenone was condensed with *o*-chlorophenylmagnesium bromide to give 9-*o*-chlorophenylfluoren-9-ol (I) which with amalgamated zinc and hydrochloric acid yielded 9-*o*-chlorophenylfluorene (II; R = Cl). Replacement of the halogen atom by the cyano-group and hydrolysis of the nitrile gave *o*-9-fluorenylbenzoic acid (II; R = CO_2H) which was cyclised to 1 : 9-phenyleneanthranyl acetate (III) by the method of Fieser and Hershberg (*J. Amer.*



(I) (II) (III) (IV) (V) (VI) (VII)

Chem. Soc., 1937, **59**, 1028). Reductive hydrolysis with zinc and sodium hydroxide yielded a hydrogenated product, probably (IV), which on dehydrogenation gave 2 : 3-benzofluoranthene (V). This dehydrogenation also occurs when the dihydro-product is passed through a column of alumina. 9 : 10-Dihydroanthracene similarly is partly converted into anthracene.

Ring-closure of the acid chloride of *o*-9-fluorenylbenzoic acid by stannic chloride yielded an orange product, m. p. 280—282°, which seemed by analysis to be 1 : 9-phenylene-10-anthrone (VII). The melting point differs considerably from that of Weiss and Knapp (*loc. cit.*), and the cause of this discrepancy is being investigated.

Elbs pyrolysis of 1-benzoylfluorene also gave 2 : 3-benzofluoranthene, but the yield was poor and the product was contaminated with an oxygenated compound, $C_{40}H_{24}O$, possibly an

ether containing two benzofluoranthene residues. Attempts to prepare the benzoylfluorene from fluorene-1-carboxyl chloride and benzene were unsuccessful, and there were indications that the chloride had condensed with fluorene nuclei in preference to benzene. The failure seems to be due to the inactivity of the benzene since the chloride readily condenses with naphthalene (Fieser and Seligman, *J. Amer. Chem. Soc.*, 1935, **57**, 2174) and with anisole. Fluorenone-1-carboxyl chloride reacts readily with benzene, presumably because the latter competes successfully with the deactivated fluorenone molecule. 1-Benzoylfluorene, however, was prepared in good yield from the acid chloride and excess of diphenylcadmium (Cason, *Chem. Reviews*, 1947, **40**, 15).

2 : 3-Benzofluoranthene is obtained in golden-yellow crystals and gives with maleic anhydride a colourless adduct, presumably (VI).

Attempts were made to synthesise 2 : 3-benzofluoranthene by converting aceanthraquinone into the dimethyl glycol and heating the latter with maleic anhydride and acetic anhydride (cf. Campbell and Gow, *J.*, 1949, 1555). The quinone and methylmagnesium iodide gave only one dimethyl glycol, which failed to react with maleic anhydride. This is a strong indication that the glycol is the *cis*-compound (cf. Campbell and Gow, *loc. cit.*) and is in harmony with the formation of the *cis*-dimethyl glycol from phenanthraquinone and methylmagnesium iodide (Criegee *et al.*, *Ber.*, 1940, **73**, 571).

Unsuccessful efforts were made to extend the work of Campbell and Gow (*loc. cit.*) by heating *trans*-7 : 8-dimethylacenaphthene-7 : 8-diol with citraconic anhydride and β-benzoylacrylic acid. The only product isolated from the last-named substance was the so-called " Pechmann dye " (von Pechmann, *Ber.*, 1882, **15**, 885) formed by the self-condensation of the β-benzoylacrylic acid.

Reductive ring-closures of carboxylic acids have been effected by a mixture of potassium iodide and hydriodic acid (Miescher and Billeter, *Helv. Chim. Acta*, 1939, **22**, 601). The method proved very convenient for converting 1-*o*-carboxybenzoylnaphthalene into a reduced product which on dehydrogenation gave 1 : 2-benzanthracene, but failed with 4- and 11-*o*-carboxybenzoylfluoranthene and 3-*o*-carboxybenzoylacenaphthene.

Some other methods for synthesising benzofluoranthenes were explored, without success. In an attempt to prepare 9-2′-keto*cyclo*hexylanthracene, 2-chloro*cyclo*hexanone was condensed with 9-anthrylmagnesium bromide (cf. Newman and Booth, *J. Org. Chem.*, 1947, **12**, 737), but the only product isolated was anthracene, presumably owing to " enolisation " (cf. Bachmann and Kloetzel, *ibid.*, 1939, **3**, 55).

Anthrone and Grignard reagents are known to yield the expected carbinols (Krollpfeiffer and Branschied, *Ber.*, 1923, **56**, 1617; Sieglitz and Marx, *Ber.*, 1923, **56**, 1619). We were, therefore, surprised to obtain from *o*-chlorophenylmagnesium bromide and anthrone, not a carbinol, but anthraquinone.

Like previous workers (*e.g.*, Pfeiffer and Blank, *J. pr. Chem.*, 1939, **153**, 249; Tucker, Whalley, and Forrest, *J.*, 1949, 3194) we found in several instances that ketones reacted with Grignard reagents only when an excess of the latter (2—3 mols.) was used.

Experimental.

All chromatographic experiments were carried out with B.D.H. alumina (Brockmann), and fluorescence observations were made under a Hanovia lamp. New substances were analysed by Drs. Weiler and Strauss (Oxford).

Synthesis of 2 : 3-*Benzofluoranthene from Fluorenone.*—*o*-Bromochlorobenzene (29·3 g.) in dry ether (80 ml.) was added dropwise with stirring to magnesium (3·2 g.) in dry ether (20 ml.). Fluorenone (9 g.) was dissolved in benzene, dry ether (50 ml.) was added, and the solution was stirred into the Grignard solution. The mixture was boiled for an hour and was then worked up in the usual way, to give an oil which on trituration with light petroleum gave solid 9-*o-chlorophenylfluoren*-9-*ol*, plates (from methanol), m. p. 140—141° (yield, 75—82%) (Found: C, 78·6; H, 4·4; Cl, 11·6. $C_{19}H_{13}OCl$ requires C, 77·9; H, 4·4; Cl, 12·0%). The alcohol shows a pale heliotrope fluorescence and gives a wine-red colour in concentrated sulphuric acid. With acetyl chloride it forms the *acetate*, prisms (from ethanol–acetic acid), m. p. 145° depressed to 120° when admixed with the alcohol (Found: Cl, 11·3. $C_{21}H_{15}O_2Cl$ requires Cl, 10·5%). The alcohol (17·8 g.) was boiled for 3 hours with lightly amalgamated zinc dust (9 g.), granulated zinc (18 g.), acetic acid (500 ml.), and concentrated hydrochloric acid (100 ml.). Filtration and concentration of the solution gave an oil which crystallised when cooled and scratched. 9-*o-Chlorophenylfluorene* crystallised in prisms (from methanol), m. p. 76—77° (14·5 g., 85%) (Found: C, 82·0; H, 4·8. $C_{19}H_{13}Cl$ requires C, 82·4; H, 4·7%). The chloro-compound (12·3 g.) was converted into the cyano-compound by heating it in a sealed tube for 24 hours at 240° with cuprous cyanide (6 g.), pyridine (15 ml.), and acetonitrile (1·5 ml.). The mixture was poured into dilute acid and was extracted with benzene. The extract was washed successively with ammonia, water, acid, and water, and the volume was then reduced. The concentrate was passed through a column which was developed with benzene. A zone with a weak violet fluorescence at the foot of the

column yielded on elution o-9-*fluorenylbenzonitrile*, compact prisms [from light petroleum (b. p. 80—100°)], m. p. 115—116° (7·5 g.) (Found : C, 90·0; H, 4·9; N, 5·2. $C_{22}H_{13}N$ requires C, 89·9; H, 4·9; N, 5·2%). A deep-violet-fluorescing zone on the column gave unchanged chloro-compound, and a violet-fluorescing zone at the top gave the *amide*, elongated prisms (from light petroleum–benzene), m. p. 142—143° (0·2 g.) (Found : C, 84·5; H, 5·3; N, 4·9. $C_{22}H_{15}ON$ requires C, 84·2; H, 5·3; N, 5·0%). Carrying out the Rosenmund reaction in the presence of copper sulphate and tolunitrile gave a higher percentage of the amide at the expense of the nitrile (cf. Koelsch and Whitney, *J. Org. Chem.*, 1941, **6**, 794).

The nitrile (9·3 g.), sodium hydroxide (3·6 g.), water (9 ml.), and ethylene glycol (36 ml.) were boiled for 24 hours. Acidification gave o-9-fluorenylbenzoic acid, plates (from acetic acid), m. p. 241—242° (8·8 g., 88%) (Found : C, 82·7; H, 4·9. Calc. for $C_{22}H_{14}O_2$: C, 83·9; H, 4·9%). The acid gives a red colour with concentrated sulphuric acid.

The acid (1 g.), acetic acid (6 ml.), acetic anhydride (5 ml.), and a trace of zinc chloride were boiled for 2 hours. Water was added to the hot solution until crystallisation occurred. The crude acetate (0·9 g.) was boiled for 22 hours with sodium hydroxide (30 ml.), toluene (10 ml.), and zinc dust (1·5 g.) which had been shaken with 0·1% copper sulphate solution. Benzene was added and the organic layer, after separation, was washed and passed through a column. A greenish-yellow band separated and on elution gave a product (0·25 g.) which was crystallised from light petroleum. Some of the crystals were separated mechanically into the orange-yellow 2 : 3-benzofluoranthene, m. p. 145—146°, identical with a sample prepared as below and with one kindly supplied by Dr. S. H. Tucker, and a colourless material, m. p. 139—140°, which was assumed to be the dihydro-compound (IV). The mixture of crystals (0·2 g.) was quantitatively dehydrogenated to 2 : 3-benzofluoranthene by boiling them for 13 hours with chloranil (0·2 g.) in sulphur-free xylene. 2 : 3-Benzofluoranthene crystallises from light petroleum in plates and forms a *picrate*, crimson prisms (from benzene), m. p. 215° (Found : N, 8·9. $C_{28}H_{15}O_7N_3$ requires N, 8·7%); and with maleic anhydride it gives an *adduct*, prisms, m. p. 220—235° (decomp.) (Found : C, 81·5; H, 4·1. $C_{24}H_{14}O_3$ requires C, 82·2; H, 4·0%).

o-9-Fluorenylbenzoic acid (0·5 g.) in dry benzene (5 ml.) and phosphous pentachloride (0·45 g.) were gently warmed and after 15 minutes stannic chloride (0·2 ml.) in dry benzene (3 ml.) was added. 30 Minutes later the mixture was decomposed with ice and hydrochloric acid, and the product (0·22 g.) crystallised from xylene. 1 : 9-o-Phenylene-10-anthrone (1 : 4-dihydro-4-keto-2 : 3-benzofluoranthene) (?) was obtained in bright orange prisms, m. p. 280—282° (decomp.) (Found : C, 89·6; H, 4·3. Calc. for $C_{22}H_{12}O$: C, 89·6; H, 4·5%).

Synthesis of 2 : 3-*Benzofluoranthene from* 1-*Benzoylfluorene*.—The acid chloride of fluorene-1-carboxylic acid reacted with anisole at room temperature in the presence of aluminium chloride, to give a good yield of 1-p-*anisoylfluorene*, prisms (from ethanol), m. p. 104—105° (Found : C, 82·7; H, 5·6. $C_{21}H_{16}O_2$ requires C, 84·0; H, 5·3%).

Anhydrous cadmium chloride (7 g.) was added in portions to the Grignard reagent prepared from magnesium (1·8 g.), bromobenzene (10 ml.), and ether (50 ml.). When the Michler ketone test showed the absence of Grignard reagent, the ether was distilled off and replaced by benzene (20 ml.). A benzene solution of fluorene-1-carboxyl chloride (2 g.) was added dropwise to the solution, and the mixture was boiled for 4 hours, and then kept overnight. Decomposition with ice and mineral acid gave a benzene extract which was washed with carbonate, then water, and dried. Removal of the solvent yielded an oil, which on trituration with light petroleum gave 1-*benzoylfluorene*, plates (from methanol), m. p. 90—91° (Found : C, 88·4; H, 5·1. $C_{20}H_{14}O$ requires C, 88·9; H, 5·2%).

1-Benzoylfluorene (3·0 g.) was pyrolysed for 15 minutes at 420° in carbon dioxide, and the residue was dissolved in benzene and chromatographed on a column 36″ × 1″. Development with benzene gave a bright yellow band from which a mixture of yellow and colourless prisms (0·75 g.), m. p. 140—220°, was obtained. The yellow crystals were separated by dissolution in boiling light petroleum and were converted into a picrate, decomposition of which gave 2 : 3-benzofluoranthene, yellow prisms (from aqueous methanol), m. p. 144—145°, in poor yield (Found : C, 94·8; H, 4·9. $C_{20}H_{12}$ requires C, 95·2; H, 4·8%).

Reactions of 1 : 2-*Benzacenaphthene*-7 : 8-*quinone*.—The quinone (Liebermann, *Ber.*, 1911, **44**, 3108) crystallised from chlorobenzene in crimson prisms, m. p. 268—270° (lit., 270°), and gave a green colour with sulphuric acid. Crystallisation from " aged " tetralin yielded pale orange prisms, m. p. 285—286°, which gave a red colour with sulphuric acid and proved to be anthracene-1 : 9-dicarboxylic anhydride (Found : C, 76·4; H, 3·4. Calc. for $C_{16}H_8O_3$: C, 77·4; H, 3·2%).

The quinone (2·0 g.) was added in portions to a Grignard solution prepared from magnesium (0·84 g.), ether (30 ml.), and methyl iodide (5·0 g.). The mixture was boiled and kept over-night. Decomposition with ice and hydrochloric acid gave 7 : 8-*dimethyl*-1 : 2-*benzacenaphthene*-7 : 8-*diol*, pale yellow needles (from ethanol), m. p. 230—231°, showing both in the solid state and in solution a violet fluorescence (Found : C, 81·1; H, 5·9. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%). The glycol (0·5 g.) was suspended in dry benzene (100 ml.) and dry lead tetra-acetate (1·0 g.) was added. After 15 minutes' shaking the mixture was treated with a few drops of ethylene glycol. The clear solution was washed and dried. Evaporation gave 1 : 9-*diacetylanthracene*, yellow needles (from aqueous acetone), m. p. 156—157° (Found : C, 81·6; H, 5·5. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·3%).

" *Pechmann Dye*."—*trans*-7 : 8-Dimethylacenaphthene-7 : 8-diol (0·1 g.), and β-benzoylacrylic acid (0·4 g.) were boiled in acetic anhydride (2 ml.) for 30 minutes. Cooling yielded the " Pechmann dye," elongated crimson prisms (0·04 g.) (Found : C, 76·1; H, 3·8. Calc. for $C_{20}H_{12}O_4$: C, 76·0; H, 4·0%).

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654. *Adsorption of the Aliphatic Acids, Acetic to Octanoic, at the Nitromethane Solution–Air Interface.*

By D. C. Jones and L. Saunders.

A study of the surface layers, at the air–solution interface, of solutions of the aliphatic acids, acetic to octanoic, in nitromethane has been made. The surface tensions of solutions of various concentrations have been determined and also the partial vapour pressures of the solvent in equilibrium with these solutions. From these results surface-excess concentrations have been calculated, and, by use of the general form of Gibbs's equation together with different conventions, in particular the U convention of Guggenheim and Adam and the *Z* convention of Fu and Bartell, the absolute surface concentrations have been evaluated. The results show that the adsorption excess plays a much smaller role in determining the absolute surface concentrations in the adsorption of surface-active materials on solution in organic solvents of this kind than in adsorption on aqueous solution. The relations between the surface and the bulk mol.-fractions corresponding to the various conventions have been examined, and it appears that a reasonable explanation of these results would be that the adsorption layer is unimolecular and that the acid molecules arrange themselves intermediately between a horizontal orientation, with their long axes parallel in the surface, and a random arrangement.

The basic method for determining concentrations of components in a reversibly adsorbed surface layer in equilibrium with a solution is still the Gibbs adsorption equation. This expresses the surface excess of solute in the layer in terms of the rate of change of surface tension of the solution with the chemical potential of solute in the bulk solution. The usual form of the equation

$$\Gamma_2 = -\frac{1}{RT} \cdot \frac{d\gamma}{d \ln a_2}$$

(Adam, "Physics and Chemistry of Surfaces," Oxford Univ. Press, 1946; $a_2 = f_2 N_2$, the activity of the solute in the bulk solution) is not applicable to more concentrated solutions. In these cases the general form of Gibbs's equation

$$\Gamma_2 - \frac{N_2}{1 - N_2}\Gamma_1 = -\frac{1}{RT} \cdot \frac{d\gamma}{d \ln a_2}$$

must be combined with another relation between Γ_1 and Γ_2, which cannot be derived thermodynamically, in order to evaluate Γ_1 and Γ_2 (Guggenheim, "Thermodynamics," Oxford Univ. Press, 1949). This second relation can only be obtained by making assumptions about the structure of the surface layer.

The work described in this paper consisted of a study of the adsorbed layer of some *n*-fatty acids at the interface between air and solutions of the acids in an organic solvent of moderately high surface tension (nitromethane). The experimental work consisted of measurements of the surface tensions and partial vapour pressures of solvent in equilibrium with solutions of various concentrations. From these results surface compositions have been evaluated, the general form of Gibbs's equation being used, together with two different conventions giving further relations between Γ_1 and Γ_2.

Experimental.

Materials.—The materials used were carefully purified and some physical properties were determined in each case. M. p.s were observed by using about 5 ml. of liquid contained in a double-jacketed tube; densities were measured by means of a single-bulb pyknometer of 5-ml. capacity; refractive indices were determined by means of a Pulfrich refractometer, and b. p.s were observed in an apparatus similar to that described by Jones and Betts (*J.*, 1928, 1177).

Water. Good distilled water was redistilled from a Bousfield still; γ^{20} 72·8 ergs cm.$^{-2}$ (cf. Harkins and Brown, *J. Amer. Chem. Soc.*, 1919, **41**, 499; 72·79); n_D^{20} 1·3330 (same as I.C.T.).

Benzene. Kahlbaum's purest benzene was fractionally frozen, dried over sodium, and distilled; it had m. p. 5·50°; d_4^{20} 0·8733.

Nitromethane. This was prepared from chloroacetic acid, sodium nitrite, and sodium carbonate; a quantity was also obtained from Kahlbaum. Both materials were dried ($MgSO_4$) and fractionally distilled, yielding products with identical physical constants: d_4^{20} 1·13130 (cf. Boyd and Copeland, *J. Amer. Chem. Soc.*, 1942, **64**, 2540; 1·13118); b. p. 101·0°; γ^{20} 36·23 ergs cm.$^{-2}$ (cf. Boyd and Copeland, *loc. cit.*, 35·78, by ring-pull method; I.C.T. value, 36·07).

Fatty acids. Kahlbaum's purest acids were fractionally frozen and the lower acids were fractionally distilled at low pressures.

TABLE I.

Properties of fatty acids.

	γ^{20}, obs.	γ^{20}, I.C.T.	γ^{20}, calc.	n_D^{20}	n_D^{20}, I.C.T.	M. p.	d_4^{20}
Acetic	27·6	27·6	27·7	1·3718	1·3715 (22·9°)	16·5°	1·0443
Propionic	26·6	26·7	26·2	1·3868	1·3873 (19·9°)	−21·5	0·9877
Butyric	26·8	26·8	26·8	1·3979	1·3977 (20·3°)	−5·8	0·9527
Valeric	27·4	—	27·4	1·4082	—	< −30	0·9348
Hexanoic	28·1	—	28·0	1·4165	1·4145 (19·6°)	−4·6	0·9227
Heptanoic	28·7	28·3	28·4	1·4229	1·4216 (19·8°)	−8·8	0·9134
Octanoic	29·2	—	28·8	1·4282	1·4268 (21·0°)	16·2	0·9060

A number of the physical properties of the acids were determined. The results are given in Table I; the surface tensions at 20° were determined by the maximum bubble pressure method and are compared in the table with the values given in I.C.T. and the values calculated from Samygin's equation (*J. Phys. Chem. U.S.S.R.*, 1937, **10**, 455), *viz.*,

$$\gamma = \left[\frac{8{\cdot}49(n^2-1)}{n^2+2} + \frac{20{\cdot}9d}{M}\right]^4$$

where n is the refractive index for the sodium D line, d the density, and M the monomeric molecular weight of the acid. These physical properties are of two types—density and refractive index which vary regularly with molecular weight, and m. p. and surface tension which show minima in the middle of the series.

Measurements of Surface Tension.—All these measurements were carried out by using apparatus immersed in a copper water-tank of 50-l. capacity, fitted with plate-glass windows, whose temperature was controlled to within ±0·02° by a toluene–mercury regulator. The usual precautions were taken to eliminate grease from the glass apparatus.

The solutions of acids in nitromethane were made up by weight. Their contact angles on soda glass were examined by Bartell and Merrill's method (*J. Physical Chem.*, 1932, **36**, 1178). Nitromethane and solutions of acetic to valeric acids had zero contact angles for both advancing and receding menisci; surface tensions of these solutions were therefore determined by Ferguson's modification of the capillary-rise method, as used by Carter and Jones (*Trans. Faraday Soc.*, 1934, **30**, 1027). Some of these results were checked by Sugden's maximum bubble pressure method (*ibid.*) and excellent agreement was found. Solutions of hexanoic to octanoic acids had variable contact angles on soda glass for advancing menisci, and we could not obtain reliable surface tensions for these solutions by Ferguson's method owing to the insensitivity of the meniscus at the tip of the capillary to small changes of pressure; we therefore used Sugden's method for all the determinations of the surface tensions of these solutions.

Measurements of Partial Vapour Pressures.—The partial vapour pressures of the components in equilibrium with the solutions were determined by a modification of Shaw and Butler's apparatus (*Proc. Roy. Soc.*, 1930, *A*, **129**, 519). A known volume (707·2 ml.) of dry, carbon dioxide-free air at atmospheric pressure was slowly displaced by pure mercury and blown through about 10 ml. of the liquid under investigation, contained in inclined bubblers. The air and vapour passed through a U-tube, to allow any liquid spray to settle, and then through a weighed receiver cooled in solid carbon dioxide and ether. Apart from the receiver, the apparatus was completely immersed in a water thermostat. The short length of glass tubing leading to the receiver was kept slightly above the thermostat temperature (25°) by means of an electrically heated coil, to prevent condensation of vapour before it reached the receiver.

The receiver consisted of a U-tube with ground-glass joints on both limbs. One of these fitted on to the vapour-pressure apparatus and the other connected to a guard tube (against carbon dioxide and water) and a sulphuric acid pulsimeter. Before the receiver was attached, air was bubbled through the solution for a few minutes, the receiver was put on and then cooled, and the measured volume of air blown through the solution by slowly filling a glass globe with mercury, between two etched marks. When the mercury reached the upper mark, the receiver was removed, stoppered, and allowed to warm to room temperature. One stopper was eased for a few seconds, to adjust the contents to atmospheric pressure, and the receiver was hung in the case of a Sartorius balance, modified to act as a semimicro-balance, and weighed against a suitable counterpoise. The total weight of distillate was usually 50—90 mg. Blank experiments with completely dry apparatus gave no measurable increase in the weight of the receiver if this procedure was carefully followed.

A slight concentration change often occurred during the determination, owing to the small amount of the solution used; if this change was appreciable, the mean of initial and final mol.-fractions was taken as representing the mol.-fraction of the solution.

The distillate from the solutions of appreciably volatile acids was analysed after being weighed, by washing it out of the receiver with a measured volume of aqueous ethanol, into a flask in which it was titrated with N/100-alkali (in a carbon dioxide-free atmosphere). Blank titrations were carried out with an equal volume of aqueous ethanol, and the proportion of acid in the distillate was estimated from previously prepared titre–composition curves for solutions of the acids in nitromethane.

Partial vapour pressures were calculated from the experimental results by the equation

$$\frac{1}{p_1} = \frac{M_1 V}{RT} \cdot \frac{1}{W_1} + \frac{1}{P}\left(1 + \frac{W_2 M_1}{W_1 M_2}\right)$$

a similar equation being used for p_2 in cases where this was measurable (M_1 and M_2 are molecular weights of nitromethane and acid, respectively; W_1 and W_2 are the weights in g. of distillate collected; V is the volume of air blown through the solution; P is the barometric pressure; R is the gas constant; p_1 is the partial vapour pressure of nitromethane).

The apparatus was first used to measure the vapour pressures of some pure liquids. Water gave a value 23·71 mm. at 25° (cf. 23·69 from I.C.T.); nitromethane gave 36·40 mm. at 25° which compares

FIG. 1.

p_1–N_2 *curves.*

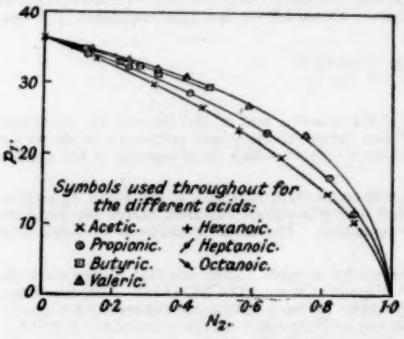
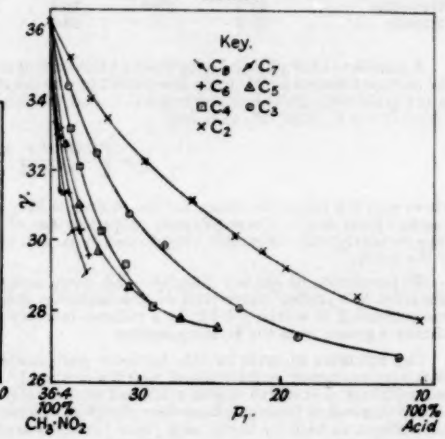


FIG. 2.



with the value 36·56 mm. calculated from an equation given by Williams (*J. Amer. Chem. Soc.*, 1925, **47**, 2644) based on direct pressure measurements. This agreement indicates that nitromethane vapour is not appreciably associated at 25°.

The results at 25° for pure acetic and propionic acids when compared with values obtained by direct pressure measurements (15·54 mm. for acetic acid, MacDougall, *J. Amer. Chem. Soc.*, 1936, **58**, 2585; 4·14 mm. for propionic acid, I.C.T.) indicated considerable association of the vapours of these acids at 25°. From the results, mean molecular weights of these two acids in the vapour phase were calculated to be 110·9 for acetic acid (corresponding to a degree of dissociation of double molecules of 0·082; cf. *idem, ibid.*, 0·081) and 91·0 for propionic acid. These mean molecular weights were used in the calculations of the partial vapour pressures of the solutions of acetic and propionic acids in nitromethane.

The partial vapour pressures of acetic acid and nitromethane in equilibrium with their solutions could be quite closely represented by the Margules integration of the Gibbs–Duhem equation:

$$p_1 = p_1^{\circ} N_1 e^{\beta N_2^2}, \qquad p_2 = p_2^{\circ} N_2 e^{\beta N_1^2}$$

where p_1°, p_2° are the vapour pressures of pure nitromethane and acetic acid, respectively, N_1, N_2 are the mol.-fractions in the solutions, and β is a constant whose value was found to be 0·23 at 25°.

All the acid solutions in nitromethane showed positive deviations from Raoult's law (see Fig. 1).

Calculation of Surface Concentrations.—The experimental values of surface tensions and partial vapour pressures of nitromethane were plotted against solution mol.-fractions, and from these, surface tensions and partial vapour pressures at round-figure mol.-fractions were determined and these were used in the subsequent calculations (see Table II).

γ–p_1 curves were then constructed (Fig. 2) and from these the value of $\Gamma_2^{(3)}$ was calculated (see Adam, *op. cit.*):

$$\Gamma_2^{(3)} = \frac{N_1}{RT} \cdot \frac{d\gamma}{d \ln a_2} = \frac{N_2}{RT} \cdot \frac{d\gamma}{d \ln a_1} = \frac{N_2}{RT} \cdot \frac{d\gamma}{d \ln p_1}$$

The values of $d\gamma/(d \ln p_1)$ were found from the γ–p_1 curves by measuring the slopes of these curves at values of p_1 corresponding to the round-figure values of N_2 and multiplying them by p_1. Some uncertainty arises in this process of graphical differentiation, and the values of $d\gamma/dp_1$ determined directly from the curves were checked by fitting empirical equations to these curves and differentiating them algebraically. Suitable equations were found to be of the rectangular hyperbola form $(\phi + b)(\pi + c) = bc$, where $\phi = \gamma_1 - \gamma$, the difference between the surface tensions of nitromethane and the acid solution; $\pi = p_1^0 - p_1$; b and c are constants; $\phi = 0$ when $\pi = 0$.

TABLE II.

			$10^{10} \times$					$10^{10} \times$	
N_2	γ.	p_1'	$\Gamma_2^{(S)}$	$\Gamma_2^{(V)}$	N_2	γ.	p_1	$\Gamma_2^{(S)}$	$\Gamma_2^{(V)}$
Acetic acid solutions.									
0·05	35·31	35·40	0·54	0·54	0·4	31·56	27·93	1·54	1·50
0·1	34·70	34·55	0·94	0·93	0·5	30·62	25·20	1·43	1·39
0·15	34·07	33·55	1·23	1·22	0·6	29·82	22·21	1·31	1·26
0·2	33·50	32·42	1·41	1·39	0·7	29·13	18·93	1·07	1·02
0·3	32·50	30·32	1·55	1·52	0·8	28·47	15·61	0·81	0·77
Propionic acid solutions.									
0·05	34·81	35·52	0·96	0·94	0·4	29·78	28·75	2·01	1·74
0·1	33·87	34·66	1·41	1·36	0·5	28·91	26·41	1·78	1·49
0·15	33·07	33·82	1·74	1·64	0·6	28·20	23·91	1·43	1·16
0·2	32·26	32·83	1·93	1·79	0·7	27·69	21·10	0·99	0·78
0·3	30·84	30·88	2·08	1·86	0·8	27·21	17·50	0·55	0·42
Butyric acid solutions.									
0·025	34·98	36·05	0·95	0·93	0·2	30·82	33·25	2·51	2·19
0·05	34·10	35·70	1·38	1·33	0·25	30·08	32·46	2·41	2·07
0·075	33·36	35·27	1·73	1·64	0·3	29·52	31·70	2·38	1·96
0·1	32·80	34·90	1·98	1·85	0·4	28·70	30·10	1·81	1·41
0·15	31·74	34·07	2·39	2·16					
Valeric acid solutions.									
0·01	35·40	36·20	0·56	0·55	0·2	30·30	33·80	2·57	2·14
0·02	35·03	36·10	1·02	1·00	0·25	29·75	33·10	2·33	1·85
0·03	34·70	36·00	1·49	1·45	0·3	29·32	32·40	1·98	1·51
0·04	34·27	35·87	1·91	1·83	0·4	28·68	30·90	1·75	1·24
0·05	33·80	35·72	2·19	2·09	0·5	28·20	29·15	1·25	0·83
0·075	32·80	35·40	2·70	2·51	0·6	27·83	27·10	0·92	0·57
0·1	32·07	35·10	2·89	2·62	0·7	27·57	24·52	0·62	0·36
0·15	31·03	34·45	2·63	2·23					
Hexanoic acid solutions.									
0·01	35·38	36·27	0·89	0·88	0·075	32·07	35·40	2·58	2·34
0·02	34·67	36·14	1·42	1·38	0·1	31·32	35·06	2·69	2·38
0·03	34·00	36·00	1·79	1·72	0·15	30·32	34·40	2·79	2·32
0·04	33·42	35·86	2·07	1·97	0·2	29·60	33·72	2·67	2·09
0·05	32·97	35·73	2·29	2·15					
Heptanoic acid solutions.									
0·01	35·37	36·24	0·82	0·81	0·05	32·40	35·64	2·53	2·34
0·02	34·55	36·09	1·54	1·49	0·075	31·03	35·27	2·57	2·29
0·03	33·80	35·94	2·14	2·04	0·1	30·21	34·90	2·55	2·30
0·04	33·07	35·79	2·36	2·21	0·15	29·42	34·30	2·72	2·18
Octanoic acid solutions.									
0·005	35·60	36·32	0·45	0·45	0·03	32·78	35·84	2·67	2·52
0·01	35·10	36·22	0·90	0·88	0·04	31·50	35·64	3·56	3·30
0·02	33·90	36·02	1·79	1·72					

Equations of this type are convenient, since on multiplication and rearrangement they can be written

$$\phi + (\phi/\pi)c + b = 0$$

so that if ϕ/π is plotted against ϕ, a straight line is obtained from which the values of the constants b and c can readily be determined. The differential coefficient is given by

$$d\phi/d\pi = -(\phi + b)/(\pi + c) = d\gamma/dp_1$$

and so by finding b and c from the straight-line plots, values of $d\gamma/dp_1$ can be calculated. The plot of ϕ/π against ϕ yielded quite good straight lines for all except the most dilute acid solutions (see Fig. 3). In general, the values of $d\gamma/dp_1$ found from these lines agreed fairly well with those obtained by measuring

directly the slopes of the γ–p_1 curves. Where any considerable divergence occurred, the values obtained from the empirical equations were preferred in the range where the ϕ/π–ϕ plots were linear.

Having determined $d\gamma/dp_1$ at various values of p_1 corresponding to the round figure values of N_2, we found the corresponding values of $\Gamma_2^{(N)}$. These were used as the starting points for subsequent calculations.

Table II shows the values of the surface tensions of the solutions in ergs/cm.^{2} at 25°, p_1 the partial vapour pressure in equilibrium with the solution at 25° in mm. of mercury, and $\Gamma_2^{(N)}$ and $\Gamma_2^{(V)}$ in g.-mols. cm.$^{-2}$, for the round-figure values of N_2:

$$\Gamma_2^{(V)} = \frac{V_1}{V_1N_1 + V_2N_2} \cdot \Gamma_2^{(N)}$$

where V_1 and V_2 are the molar volumes of nitromethane and acid, respectively (Adam, *op. cit.*).

FIG. 3.

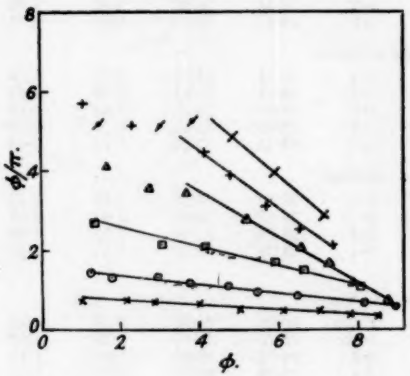
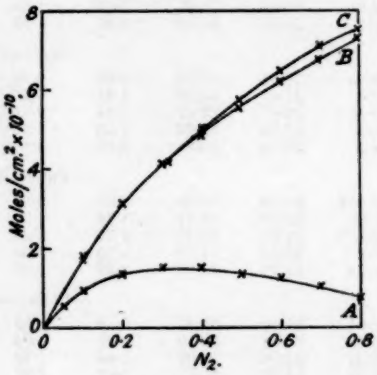


FIG. 4.
Adsorption of acetic acid.



A. $\Gamma_2^{(V)}$.
B. Z_2, *vertical orientation.*
C. Z_2'', *horizontal orientation.*

DISCUSSION.

From the values of the surface-excess concentrations were calculated values of the absolute surface concentrations and mol.-fractions of acid in the surface layer, two conventions being used.

Convention I. This is Adam and Guggenheim's U-convention (*Proc. Roy. Soc.*, 1933, *A*, **139**, 218) which assumes that the areas per molecule of each component in the surface layer are independent of the bulk solution concentration and that

$$\Gamma_1A_1 + \Gamma_2A_2 = 1$$

where A_1 and A_2 are the areas per g.-mol. in the surface of the solvent and solute, respectively. This equation is solved simultaneously with the general Gibbs equation, giving

$$\Gamma_2^{(U)} = \frac{\Gamma_2^{(N)} + N_2/A_1}{1 + N_2[(A_2/A_1) - 1]}$$

The index (U) is used to indicate Γ values calculated by this convention. $\Gamma_2^{(U)}$, unlike $\Gamma_2^{(N)}$ and $\Gamma_2^{(V)}$, is an absolute surface concentration and not an excess concentration.

To obtain numerical values of $\Gamma_2^{(U)}$, it is clearly necessary to assign values to A_1 and A_2. This can only be done by making some assumptions about the surface layer structure. We have assumed that the nitromethane has no definite orientation; *i.e.*, we have put $A_1 = 0{\cdot}120 \times 10^{16}$ cm.^{2} per g.-mol., corresponding to an area per molecule of 20·0 sq. A., which is equal approximately to the two-thirds power of the volume of the nitromethane molecule at 25°, and that the acid molecule has (*a*) an upright orientation in the surface layer, giving a value of A_2 corresponding to an area per molecule of 20·5 sq. A., ($\Gamma_2^{(U)}$); (*b*) no definite orientation, in

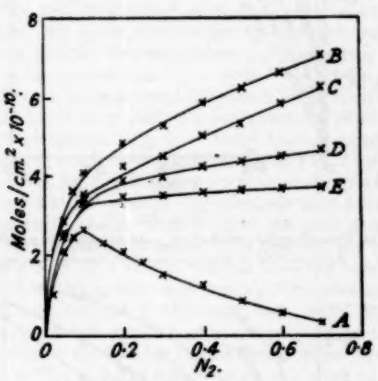
which case values of A_2 are taken corresponding to an area per molecule equal to the two-thirds power of the volume per molecule (A_2' and $\Gamma_2^{(V')}$).

The corresponding surface mol.-fractions ${}^{V}n_2$ and ${}^{V'}n_2$ were then calculated.

Convention II. This is the convention used by Fu and Bartell (*J. Phys. Colloid Chem.*, 1950, **54**, 537). The Adam and Guggenheim V-convention is used to calculate the surface-excess concentration of solute, and in order to obtain the absolute surface concentration Z_2, a quantity B, the concentration of solute which would have been present in the surface layer if no adsorption had occurred, is added to $\Gamma_2^{(V)}$. Values of B can only be obtained if assumptions are made about the thickness of the surface layer. We have investigated three different assumptions, all of which consider the surface layer as unimolecular with respect to acid: (*a*) The acid molecules are oriented perpendicularly to the surface, the surface layer thickness d being equal to the length of the acid molecule; this gives B and Z_2. (*b*) The acid molecules have no definite orientation, d' = (volume per acid molecule)$^{1/3}$; this gives B' and Z_2'. (*c*) The acid molecules are oriented horizontally, *i.e.*, parallel to the surface, $d'' = \sqrt{20{\cdot}5}$; this gives B'' and Z_2''.

FIG. 5.

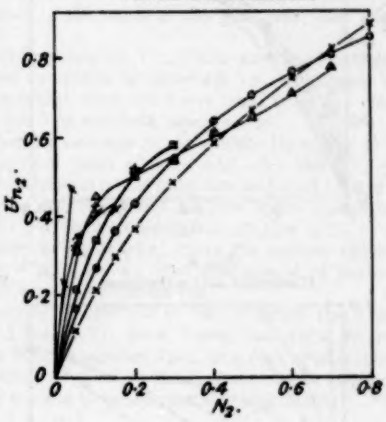
Adsorption of valeric acid.



A. $\Gamma_2^{(V)}$
B. Z_2 } *vertical orientation.*
C. $\Gamma_2^{(V)}$
D. Z_2', *random orientation.*
E. Z_2'', *horizontal orientation.*

FIG. 6.

Vertical acid orientation.



The calculations of the surface concentrations Z_2, and the corresponding Z_1 values were made following the method of Fu and Bartell; the Z_2'' and Z_1' values were calculated in a somewhat similar manner and from these the corresponding surface mol.-fractions of the acids ($^{Z}n_2$, $^{Z'}n_2$ and $^{Z''}n_2$) were then obtained.

TABLE III.

Molecular dimensions used in the calculations.

	d_4^{25}, g./cm.³	V_1, cm.³/g.-mol.	V_1, A.³/mol.	$V_1^{2/3}$, A.³/mol.	$V_1^{1/3}$, A./mol.	$10^{-16}A_1$, cm.²/g.-mol.
Nitromethane	1·1313	53·9	89·5	20·0	4·47	0·120

Acid.	V_2, cm.³/mol.	$10^{-16}A_2$, cm.²/g.-mol.	$10^{-16}A_2'$, cm.²/g.-mol.	$10^8 d$, cm.	$10^8 d'$, cm.	$10^8 d''$, cm.
Acetic	57·5	0·123	0·125	4·67	4·57	4·53
Propionic	75·0	,,	0·150	6·10	5·00	,,
Butyric	92·4	,,	0·175	7·48	5·35	,,
Valeric	109·1	,,	0·194	8·85	5·66	,,
Hexanoic	125·6	,,	0·212	10·18	5·93	,,
Heptanoic	142·4	,,	0·230	11·51	6·18	,,
Octanoic	159·0	,,	0·246	12·86	6·41	,,

The difference between conventions I and II is that if ordinary molecular dimensions are used, the U-convention assumes a film unimolecular with respect to both components, whereas convention II assumes a film unimolecular with respect to the "longer" component but multimolecular with respect to the "shorter" one.

In the case of horizontal acid orientation, the two conventions lead to about the same result owing to the molecular dimensions involved (see Table III). This case has therefore only been worked out for convention II.

FIG. 7.
Vertical acid orientation.

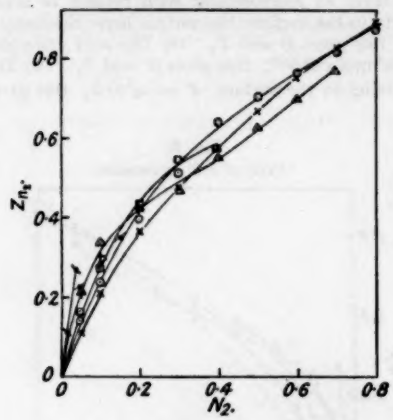


FIG. 8.
Random acid orientation.

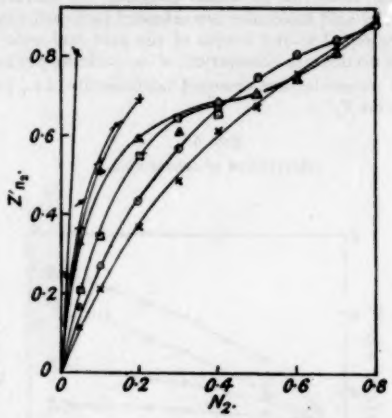


FIG. 9.
Horizontal acid orientation.

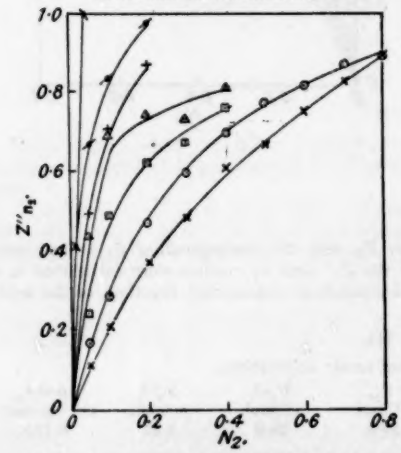
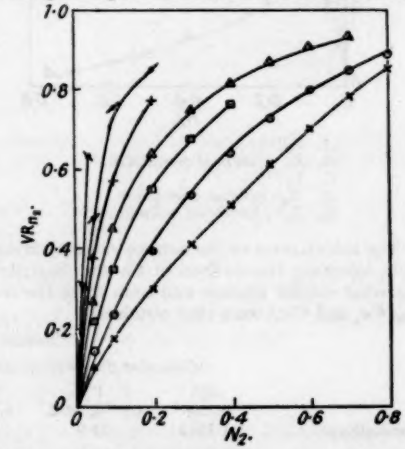


FIG. 10.
Van Rysselberghe convention; no orientation assumed.



Some of our results of the calculations of surface excess concentrations, Γ_2, and absolute surface concentrations are shown in Figs. 4 and 5. These bring out the major difference between the adsorption of surface-active materials on solutions in organic solvents and adsorption on aqueous solutions. The absolute surface concentration of acid, Z_2, in the former case is seen to be largely controlled by the bulk concentration, the adsorption excess playing a much smaller role in determining Z_2 than in aqueous adsorption.

Figs. 6—10 illustrate the relations between the surface mol.-fractions of acid, calculated

according to the various conventions, and the bulk mol.-fraction. It is seen that the various conventions that are considered all give a surface mol.-fraction which increases steadily with bulk mol.-fraction and, in this respect, all the conventions and assumptions of acid orientation considered yield reasonable results for any particular nitromethane–acid system.

The orientation assumptions are, however, sharply differentiated by the character of the plots obtained when the whole series of acid–nitromethane systems are considered together. It is seen that the assumption of vertical acid orientation (${}^{U}n_2$ and ${}^{Z}n_2$, Figs. 6 and 7) leads to a set of curves which are brought very close together for the whole series of acids; in the case of the *Z*-convention (II), this effect is more pronounced than that in the U-convention (I), since in the former case the thickness of the surface layer is supposed to be determined by the long dimension of the oriented acid and this increases steadily with the length of the chain; the adsorption space is thus steadily increased and it is supposed that the nitromethane molecule can be adsorbed to a thickness of several molecules: *e.g.*, in the case of octanoic acid (see Table III) a surface layer nearly three molecules thick with respect to nitromethane is implied by the *Z* convention.

This grouping together of the n_2–N_2 curves seems unlikely to be correct. In solutions of the higher acids in which the surface tension is within a dyne of the value for the pure acid, the assumption of vertical orientation of acid leads to quite low values of n_2; *e.g.*, heptanoic acid, $N_2 = 0{\cdot}15$, $\gamma = 29{\cdot}42$, *i.e.*, is within $0{\cdot}72$ erg cm.$^{-2}$ of the value of the pure acid, and yet ${}^{U}n_2$ and ${}^{Z}n_2$ are only $0{\cdot}42$ and $0{\cdot}35$, respectively.

If no definite assumption is made about the acid orientation, *i.e.*, if it is considered completely random, the n_2–N_2 curves are spaced out more as would be expected, *i.e.*, the higher acids show a greater deviation from a straight-line relation than the lower ones (Fig. 8). In the case of heptanoic acid $N_2 = 0{\cdot}15$, ${}^{U'}n_2$ and ${}^{Z'}n_2$ are $0{\cdot}68$ and $0{\cdot}64$, respectively.

If the acid molecule is assumed to be horizontally oriented in the surface layer, the U- and the *Z*-convention yield almost identical results with these systems and only the ${}^{Z''}n_2 - N_2$ results are shown (Fig. 9). Apart from some irregularities in the more concentrated valeric acid solutions (which have been left out of Fig. 9 for the sake of clarity), an even better separation of the curves for the different systems is obtained. For the heptanoic acid solution of $N_2 = 0{\cdot}15$, ${}^{Z''}n_2$ is now $0{\cdot}9$, and for the octanoic acid solution of $N_2 = 0{\cdot}04$, where the surface tension is 2 ergs cm.$^{-2}$ greater than that of the pure acid, ${}^{Z''}n_2 = ca.\ 1$. The assumption of horizontal orientation therefore seems to exaggerate the separation of the curves.

The idea of a direct relation between surface concentration or mol.-fraction and surface-tension lowering was suggested by Matthews and Stamm (*J. Amer. Chem. Soc.*, 1924, **46**, 1071). Van Rysselberghe (*J. Physical Chem.*, 1938, **42**, 1021) suggested that, as a first approximation, the surface mol.-fraction of a solute could be taken as equal to the surface-tension lowering of the solution divided by the difference of surface tension between the two components: ${}^{VR}n_2 = (\gamma_1 - \gamma)/(\gamma_1 - \gamma_2)$ or $n_2\gamma_2 + n_1\gamma_1 = \gamma$ since $n_1 + n_2 = 1$.

We have plotted a set of values of ${}^{VR}n_2$ calculated by this method (Fig. 10); no assumptions need be made about orientations in the surface layer. It is seen that the ${}^{VR}n_2$–N_2 curves form a group which, as would be expected, show a regularly increasing deviation from the straight-line relation as the length of the hydrocarbon chain in the acid is increased. On comparing the ${}^{VR}n_2$–N_2 curves with the others, it is seen that they are situated intermediately between the random and horizontal orientation plots. If the validity of Van Rysselberghe's approximation can be accepted, then the acid molecules in the surface layer would appear to be oriented between a completely random and a horizontal arrangement (cf. Taubmann, *Acta Physicochem. U.S.S.R.*, 1936, **5**, 555).

It is interesting that this is also the conclusion reached from the preceding discussion of the various conventions based on the fundamental theory of Gibbs; the acid molecules on entering the surface layer encounter forces which tend to orient them so that their long axes are parallel to the surface, but which are inadequate to produce a completely ordered layer.

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THE SCHOOL OF PHARMACY AND QUEEN MARY COLLEGE,
UNIVERSITY OF LONDON. [*Received, March 19th*, 1951.]

655. *Nucleotides. Part VIII.** cyclo*Nucleoside Salts. A Novel Rearrangement of Some Toluene*-p-*sulphonylnucleosides.*

By V. M. Clark, A. R. Todd, and J. Zussman.

Toluene-*p*-sulphonylation of 2′ : 3′-*iso*propylidene adenosine (I) yields two isomeric products, one the normal toluene-*p*-sulphonyl ester (II) and the second an ionic compound containing the toluene-*p*-sulphonate anion. The ester (II), on being heated in acetone solution, is rapidly converted into the ionic isomer which yields an ionic iodide on treatment with sodium iodide. Chemical evidence, coupled with *X*-ray crystallographic analysis, shows that these ionic compounds are salts of 2′ : 3′-*iso*propylidene 3 : 5′-*cyclo*-adenosine (III and IV) in which a new ring has been formed by intramolecular alkylation. *cyclo*-Derivatives are not produced from the toluene-*p*-sulphonyl derivatives of inosine or uridine, but 2′ : 3′-*iso*propylidene 5′-toluene-*p*-sulphonyl cytidine rearranges readily to the ionic 2′ : 3′-*iso*propylidene O^2 : 5′-*cyclo*cytidine toluene-*p*-sulphonate (V). The formation of these *cyclo*nucleoside salts affords independent proof of the β-configuration of the natural ribonucleosides.

During investigations into the synthesis of nucleotides and related phosphates of carbohydrate derivatives, we have devoted some attention to the condensation of halogeno-derivatives of carbohydrates and nucleosides with silver salts of phosphoric and polyphosphoric acids. The reaction between a silver diaryl or diaralkyl phosphate and a halogeno-sugar was first studied by Zervas (*Naturwiss.*, 1939, **27**, 317), and the method has been used for the preparation of glucose-1 phosphate (Zervas, *loc. cit.*; Wolfrom, Smith, Pletcher, and Brown, *J. Amer. Chem. Soc.*, 1942, **64**, 23) and galactose-1 phosphate (Reithel, *ibid.*, 1945, **67**, 1056). For the synthesis of simple nucleotides, condensation of the iodo-derivative of a nucleoside (*e.g.*, 5′-iodo-5′-deoxyadenosine) with silver dibenzyl phosphate seemed a feasible alternative to the route using a suitably protected nucleoside and dibenzyl chlorophosphonate (Baddiley and Todd, *J.*, 1947, 648). The method seemed particularly attractive for, if successful, it would open the way to the synthesis of dinucleotides by condensation of halogeno-nucleosides with the silver salts of nucleotide monobenzyl esters, for which convenient methods of preparation are now available (Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815; Clark and Todd, *J.*, 1950, 2023, 2030).

The displacement of the toluene-*p*-sulphonyl residue from carbohydrate derivatives by anionic attack, particularly by the iodide ion (Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366) is well known, and it was hoped to obtain the requisite iododeoxynucleosides in this way from the corresponding toluene-*p*-sulphonylated nucleosides. Thus, 2′ : 3′-*iso*propylidene 5′-toluene-*p*-sulphonyl uridine reacts with sodium iodide (Levene and Tipson, *J. Biol. Chem.*, 1934, **106**, 113) to give the corresponding 5′-iodo-5′-deoxy-compound, which can be condensed with silver dibenzyl phosphate to yield the 5′-(dibenzyl phosphate); this, after hydrogenolysis of the benzyl groups and hydrolysis of the *iso*propylidene residue, gives uridine-5′ phosphate (experiment by Dr. J. Davoll), identical with the product prepared by an alternative route (Michelson and Todd, *J.*, 1949, 2476).

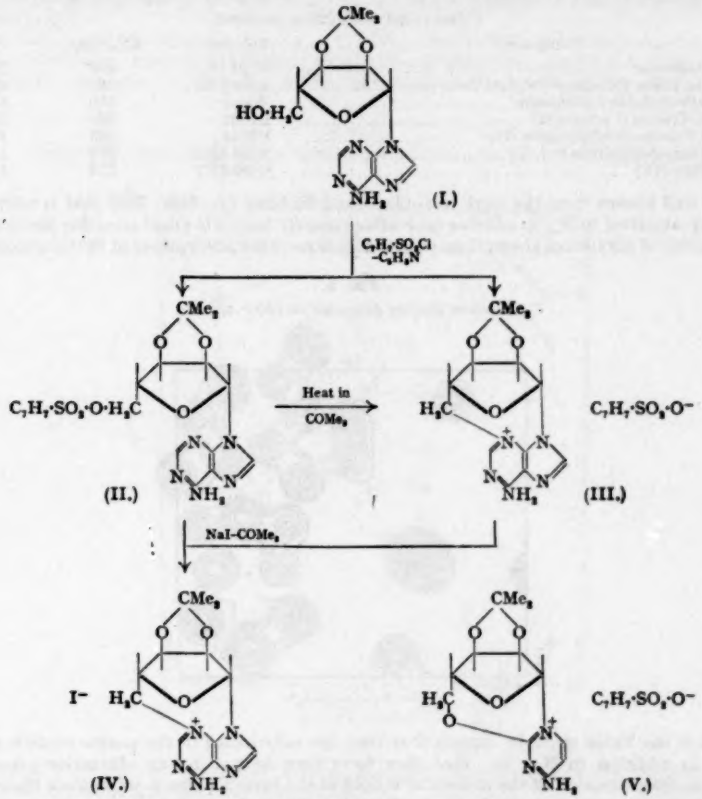
It was expected that the performance of an analogous series of reactions with adenosine in place of uridine would yield muscle adenylic acid, but this has not proved to be the case. Several groups of workers (*e.g.*, Satoh and Makino, *Nature*, 1951, **167**, 238; Baddiley, Trauth, and Weygand, *ibid.*, p. 360) have claimed the preparation of 2′ : 3′-*iso*propylidene 5′-toluene-*p*-sulphonyl adenosine but the product has yet to be adequately characterised and the work described herein shows that those structural proofs based on this intermediate leave not a little to be desired.

After the reaction between 2′ : 3′-*iso*propylidene adenosine (I) and toluene-*p*-sulphonyl chloride in pyridine solution it was found possible to isolate two products, each having the expected elementary composition, the one behaving as a covalent compound and the other as an ionic compound. When heated with sodium iodide in acetone, the two toluene-*p*-sulphonyl derivatives gave the same iodo-derivative, which contained ionic iodine. That the transformation from the covalent compound to the ionic one was associated with the toluene-*p*-

* Part VII, *J.*, 1951, 1867.

sulphonate was shown by heating the covalent compound, 2′ : 3′-*iso*propylidene 5′-toluene-*p*-sulphonyl adenosine, in acetone solution, whereupon it was converted into the isomeric ionic toluene-*p*-sulphonate.

The covalent toluene-*p*-sulphonate can only be obtained under rigidly controlled conditions. The rearrangement to the ionic product proceeds slowly at room temperature (62% conversion after 1 week in acetone solution) but rapidly when heated (68% after 1½ hours in acetone solution



at 100°; almost quantitative after 1 hour in dioxan solution under reflux). Paper chromatography established the essential homogeneity of the covalent toluene-*p*-sulphonate, photography in ultra-violet light disclosing a single spot (R_P = 0·86 in ethanol–ammonia–water). Under the same conditions, the ionic toluene-*p*-sulphonate gave a single purine spot (R_P = 0·68) together with a spot corresponding to the anion of toluene-*p*-sulphonic acid (R_P = 0·83), detected by the iodide–iodate–starch spray developed in this laboratory (Long, Quayle, and Stedman, *J.*, 1951, 2197). Similar observations were made in two other solvent systems. It seemed clear that this rearrangement was bound up with the basic character of the adenine nucleus present in adenosine, for 2′ : 3′-*iso*propylidene inosine, which contains a hypoxanthine (6-hydroxypurine) nucleus, gives a normal toluene-*p*-sulphonyl ester (Levene and Tipson, *J. Biol. Chem.*, 1935, **111**, 313) which does not appear to undergo rearrangement to an ionic compound. This suggests that the toluene-*p*-sulphonylated adenosine derivative, being at once a base and the ester of a strong acid, can undergo rearrangement involving either alkylation (which could be intramolecular or intermolecular) or elimination of toluene-*p*-sulphonic acid to give the salt of a riboseen derivative in which there would be a double bond

between $C_{(4')}$ and $C_{(5')}$ in the adenosine molecule. The latter possibility can be ruled out on spectroscopic ground. The infra-red spectrum of the ionic compound showed no band indicative of the grouping $^{+}O\!>\!C\!=\!CH_2$. From the Table it can be seen that the ultra-violet absorption maxima of the ionic toluene-*p*-sulphonate and iodide differ markedly in their position from that of adenosine itself or the covalent toluene-*p*-sulphonate.

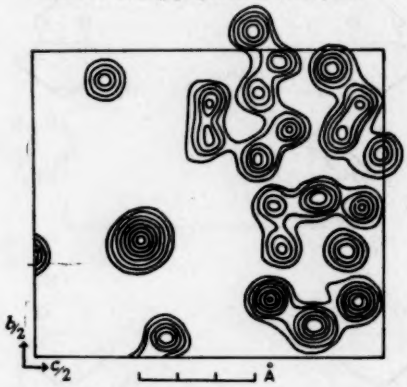
Ultra-violet absorption maxima.

Compound	Solvent	$\lambda_{max.}$ (mμ.)	$\epsilon_{max.}$
9-Methyladenine	N/20-HCl	260	14,140
9-Methyladenine toluene-*p*-sulphonate (salt)	N/20-HCl	260	13,790
2′ : 3′-*iso*Propylidene adenosine	Water	259	14,800
2′ : 3′ : 5′-Triacetyl adenosine	EtOH	260	14,180
Covalent toluene-*p*-sulphonate (II)	EtOH	263	12,350
Ionic toluene-*p*-sulphonate (III)	N/20-HCl	272	16,310
Ionic iodide (IV)	N/20-HCl	272	14,900

It is well known from the work of Gulland and Holiday (*J.*, 1936, 768) that substitution in the group attached to $N_{(9)}$ in adenine derivatives usually has little effect on either the position or the intensity of maximum absorption, so that the ultra-violet absorptions of the ionic compounds

FIG. 1.

Electron density projected on (100) *plane.*



recorded in the Table strongly suggest that they are substituted in the purine nucleus at some position in addition to $N_{(9)}$, *i.e.*, that they have been formed by an alkylation process. A cryoscopic determination of the molecular weight of the ionic toluene-*p*-sulphonate showed that the alkylation must be intramolecular; the value obtained was 240, which compares with a calculated formula weight of 461 for 2′ : 3′-*iso*propylidene 5′-toluene-*p*-sulphonyl adenosine (II). It follows that the ionic toluene-*p*-sulphonate is formed as a result of an intramolecular alkylation and an examination of space models suggests that the alkylation would be most likely to occur on $N_{(3)}$ in the pyrimidine nucleus since this atom can come into close proximity to $C_{(5')}$ in the sugar residue. That this is indeed the case, and that in these ionic derivatives $C_{(5')}$ is bonded to $N_{(3)}$, *i.e.*, that the ionic toluene-*p*-sulphonate is (III) and the iodide (IV), has been conclusively established by *X*-ray crystallographic analysis. The *X*-ray study was carried out on the ionic iodide which formed needles of approximately 0·03-mm. diameter. From oscillation and Weissenberg photographs, the space group and cell dimensions were found to be $P2_12_12_1$; $a = 5{\cdot}4$, $b = 15{\cdot}4$, $c = 18{\cdot}1$ Å. The specific gravity of the crystals was 1·81, which corresponds to a unit cell weight of 1640. This confirms that the re-arrangement is not intermolecular for, if it were, the weight of the structural unit would be *ca.* 800 and this would require but two asymmetric units per cell which is impossible in this particular space group.

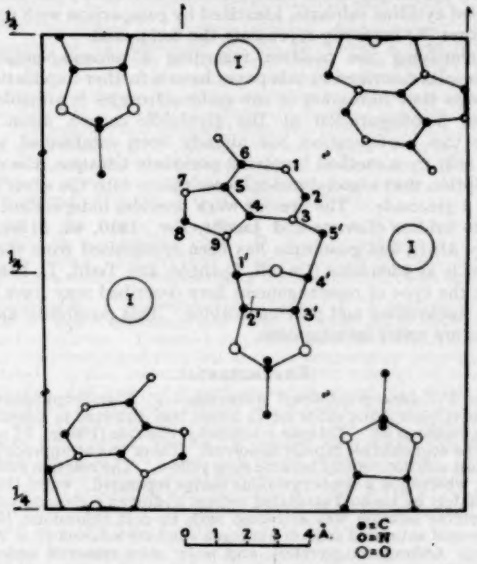
Intensities of " zero-layer " reflections were estimated visually on Weissenberg photographs, the crystal being rotated about the " *a* " crystallographic axis (the needle axis). The normal

" heavy atom " method of structural analysis was applied and this resulted in the projected electron-density map (Fig. 1). This shows clearly the general configuration of the molecule, and a three-dimensional scale model constructed on the basis of the approximately known bond lengths and angles fits the projection almost exactly. The model consistent with the projection is that of the iodide of 2′ : 3′-*iso*propylidene 3 : 5′-*cyclo*adenosine (IV) * in which (*a*) $C_{(1')}$ is coplanar with the purine ring, (*b*) the plane of the furanose ring is at an angle of *ca.* 100° with that of the purine ring, and (*c*) the approach of $C_{(5')}$ to $N_{(3)}$ is sufficiently close to indicate normal bond formation.

From the calculated distances $C_{(1')}$–$C_{(5')}$, $C_{(1')}$–$N_{(3)}$, based on observed distances in cytidine (Furberg, *Acta Cryst.*, 1950, **3**, 325) and adenine hydrochloride (Broomhead, *ibid.*, 1948, **1**, 324), the separation between $C_{(5')}$ and $N_{(3)}$ in the direction of the " *a* " axis is calculated to be

FIG. 2.

Structure as viewed along the " a " axis, showing one molecule and its environment.



approximately 1·0 Å. As the projected $C_{(1')}$–$N_{(3)}$ separation is 1·15 Å, the actual approach distance of $C_{(5')}$ and $N_{(3)}$ is approximately 1·5 Å.

Further *X*-ray analysis, together with refinement of this projection, is in progress in order to complete the structural determination.

This remarkable rearrangement of a nucleoside toluene-*p*-sulphonyl ester is not restricted to the case of adenosine. Although, as mentioned above, the 2′ : 3′-*iso*propylidene 5′-toluene-*p*-sulphonates of inosine and uridine behave as normal alkyl toluene-*p*-sulphonates and do not rearrange, isomerisation to an ionic species is observed in the case of the corresponding cytidine ester. Here as in adenosine the presence of the amino-group at $C_{(6)}$ in the pyrimidine ring is the decisive factor. Experimentally the cytidine case is more difficult to study, since toluene-*p*-sulphonylation of 2′ : 3′-*iso*propylidene cytidine yields a mixture of covalent $O_{(5')}$ and *N*-toluene-*p*-sulphonyl derivatives. However, the mixture can be used satisfactorily for further work since only the $O_{(5')}$-derivative can undergo the rearrangement involved. The mixed toluene-*p*-sulphonates dissolved readily in acetone and when the solution was heated at 100° for

* The nomenclature of such substances as (III) and (IV) presents considerable difficulty and it is proposed to refer to compounds of this type in which an additional ring has been formed as salts of " *cyclo*nucleosides," the atoms joined together to form the new ring being specified. This allows precise definition of the compounds and as far as can be seen avoids confusion.

15 minutes a crystalline isomeric compound separated which was ionic in character and which corresponded in amount to some 60% of the mixed esters. As in the adenosine case, this substance was a product of intramolecular alkylation since ebullioscopic determination of the molecular weight gave a value 205, the formula weight of 2′ : 3′-*iso*propylidene 5′-toluene-*p*-sulphonyl cytidine being 437. On stereochemical grounds it seemed hardly possible that the alkylation could have involved either of the ring-nitrogen atoms, but the proximity of $C_{(5')}$ to the oxygen atom attached to $C_{(2)}$ of the pyrimidine cycle suggested that in this instance alkylation had occurred on oxygen, *i.e.*, that the ionic compound was the toluene-*p*-sulphonate of 2′ : 3′-*iso*propylidene O^2 : 5′-*cyclo*cytidine (V).

It is well known that quaternary salts of 2-alkoxypyrimidines [to which class the compound (V) belongs] are readily dealkylated by acids, yielding the corresponding 2-hydroxypyrimidines (cf. Hilbert *et al.*, *J. Amer. Chem. Soc.*, 1930, **52**, 2001, 4489; 1936, **58**, 60). Pyrimidine derivatives alkylated on nitrogen, however, are very stable substances, and regeneration from them of the parent pyrimidines is impossible by this method. These facts offered a convenient method of establishing the nature of our ionic cytidine derivative; on being heated with dilute sulphuric acid it yielded cytidine sulphate, identified by comparison with an authentic specimen. It follows that structure (V) correctly represents the compound.

In addition to clarifying the position regarding 5′-toluene-*p*-sulphonyl esters of the ribonucleosides, the results described in this paper have a further implication. Examination of molecular models shows that formation of the *cyclo*nucleosides is possible only if the original nucleosides have the β-configuration at the glycosidic carbon atom. That the natural ribonucleosides have this configuration has already been established by Davoll, Lythgoe, and Todd (*J.*, 1946, 833) by a method involving periodate titration, the conclusion resting on the reasonable assumption that α-acetobromoglucose reacts with the silver salt of 2 : 8-dichloroadenine to produce a β-glucoside. The present work provides independent proof, since cytidine can be converted into uridine (Levene and Jacobs, *Ber.*, 1910, **43**, 3159), and adenosine into inosine (*Idem*, *ibid.*, p. 3161), and guanosine has been synthesised from the same 2 : 8-dichloroadenine D-ribofuranoside as adenosine (Davoll, Lythgoe, and Todd, *J.*, 1948, 1685).

It is possible that the type of rearrangement here described may have some counterpart in the chemistry of the nucleotides and polynucleotides. This possibility and other applications of the *cyclo*nucleosides are under investigation.

Experimental.

2′ : 3′-iso*Propylidene 5′-Toluene*-p-*sulphonyl Adenosine*.—2′ : 3′-*iso*Propylidene adenosine (2·322 g.; dried at 110°/0·1 mm. over phosphoric oxide for 12 hours) was dissolved in anhydrous pyridine (25 c.c.) at 40°, and the solution cooled in ice. Toluene-*p*-sulphonyl chloride (1·60 g., 1·1 equivs.) was added and the mixture shaken as the acid chloride rapidly dissolved. There was no appreciable rise in temperature but the initially colourless solution rapidly became deep yellow. The reaction mixture was kept at room temperature overnight, whereupon a semi-crystalline sludge separated; water (10 c.c.) was then added, followed almost immediately by ice-cold saturated sodium hydrogen carbonate solution (100 c.c.). The opalescent aqueous pyridine solution was extracted with ice-cold chloroform (3 × 100 c.c.), and the extract washed with ice-cold saturated sodium hydrogen sulphate solution (2 × 200 c.c.) and then with ice-water (2 × 200 c.c.). Chloroform, pyridine, and water were removed under reduced pressure at room temperature; subsequent evacuation to 0·01 mm. left a pale yellow resin (2·645 g., 76%) which was taken up in dry chloroform (50 c.c.) and filtered from insoluble material (50 mg.). Light petroleum (100 c.c.; b. p. 60—80°) was added and the solution left at 0° overnight; a colourless resin was deposited. The mother-liquor was decanted, the resin washed with light petroleum and the flask evacuated, whereupon the resinous 2′ : 3′-iso*propylidene 5′-toluene*-p-*sulphonyl adenosine* formed a foam which crumbled to an off-white amorphous powder (1·509 g., 43%). This product softened between 210° and 230° and decomposed with effervescence at 252° (Found, in material dried at 78°/15 mm. for 5 hours: C, 52·2; H, 4·9; N, 15·0. $C_{20}H_{23}O_6N_5S$ requires C, 52·1; H, 5·0; N, 15·2%).

2′ : 3′-*iso*Propylidene 5-toluene-*p*-sulphonyl adenosine dissolved in cold dilute hydrochloric acid and was reprecipitated on addition of sodium carbonate solution. Passage of gaseous hydrogen chloride into its ethereal solution resulted in the formation of a gel; from chloroform, the hydrochloride separated as a hygroscopic resin which rapidly became pink in air.

Paper chromatography (Whatman No. 1), with an ethanol–ammonia–water system (80 : 4 : 16), indicated that the product was homogeneous, a single spot (R_F = 0·86) being detectable by photography in ultra-violet light. When a *tert.*-butanol–acetic acid–water (5 : 4 : 1) solvent mixture was used, the R_F value was 0·86.

Evaporation of the mother-liquor left after precipitation of the toluene-*p*-sulphonyl derivative (above) yielded a yellow resin (0·299 g.), decomposing at 242° (Found, in material dried for 8 hours at 78°/15 mm.: N, 14·2. Calc. for monotoluene-*p*-sulphonyl derivative: N, 15·2; Calc. for a ditoluene-*p*-sulphonyl derivative: N, 11·4%).

Rearrangement of 2′ : 3′-iso*Propylidene 5′-Toluene*-p-*sulphonyl Adenosine*.—2′ : 3′-*iso*Propylidene 5-toluene-*p*-sulphonyl adenosine (0·190 g.) was dissolved in pure dry acetone (15 c.c.), and the clear

solution sealed in a Carius tube. On being placed in a bath at 100°, the solution rapidly became opalescent and a crystalline solid separated in quantity within 20 minutes. After 1½ hours at 100° the solid (130 mg.) was filtered off and dried. The product, 2′ : 3′-iso*propylidene* 3 : 5′-cyclo*adenosine toluene*-p-*sulphonate*, was extremely soluble in cold water, and insoluble in hot acetone and chloroform. Recrystallised from aqueous ethanol it formed colourless monoclinic prisms, m. p. 296° (decomp.) (Found, in material dried at 78°/15 mm. for 4 hours: C, 52·2; H, 4·7; N, 15·5. $C_{20}H_{23}O_6N_5S$ requires C, 52·1; H, 5·0; N, 15·2%).

The same product was obtained in almost quantitative yield by heating the original toluene-*p*-sulphonyl derivative under reflux in dioxan for 1 hour or by keeping it (163 mg.) in dry acetone at room temperature for 1 week (104 mg. deposited).

Paper chromatography (Whatman No. 1) of the product with ethanol–ammonia–water (80 : 4 : 16) gave a single purine spot (R_P = 0·68), detected by photography in ultra-violet light, together with a spot corresponding to the anion of toluene-*p*-sulphonic acid (R_P = 0·83) detected by the iodide–iodate–starch spray. In *tert.*-butanol–acetic acid–water (5 : 4 : 1) the purine component had R_P = 0·75, and the acid component R_P = 0·50.

Cryoscopic determination in water gave the molecular weight as 240 ($C_{20}H_{23}O_6N_5S$ requires *M*, 461); the Van't Hoff factor is therefore 2, as required by a uni-univalent ionic species.

Interaction of 2′ : 3′-iso*Propylidene* 5′-*Toluene*-p-*sulphonyl Adenosine and Sodium Iodide.*—2′ : 3′-*iso*Propylidene 5′-toluene-*p*-sulphonyl adenosine (1·2 g.), anhydrous sodium iodide (1·0 g.), and dry acetone (20 c.c.), were kept (sealed tube) at 100° for 2 hours. The solution, initially clear, rapidly became opalescent and a mixture of glistening needles and a micro-crystalline product separated. This was collected (1·55 g.) and shown to consist of sodium toluene-*p*-sulphonate (theor., 0·503 g.) and the iodide of the *cyclo*purine glycoside. The mixed solids were dissolved in water (50 c.c.), and the acetone mother-liquors added. This solution was extracted once with chloroform (25 c.c.), boiled with charcoal, filtered, evaporated to a small bulk (5 c.c.), and left at 0° overnight. 2′ : 3′-iso*Propylidene* 3 : 5′-cyclo*adenosine iodide* separated as colourless needles (0·55 g.) and, recrystallised from aqueous ethanol, had m. p. 277° (decomp.) (Found, in material dried at 78°/15 mm. for 5 hours: C, 37·5; H, 3·6; N, 17·0; I, 30·9. $C_{13}H_{14}O_3N_5I$ requires C, 37·4; H, 3·9; N, 16·8; I, 30·4%).

The aqueous solution of the iodide, on addition of silver nitrate solution, gave an immediate precipitate of silver iodide in quantitative yield. 2′ : 3′-*iso*Propylidene 3 : 5′-*cyclo*adenosine iodide could also be obtained by adding an equivalent of sodium iodide to a cold aqueous solution of the corresponding toluene-*p*-sulphonate and concentrating the solution to a small bulk at room temperature.

Toluene-p-*sulphonylation of* 2′ : 3′-iso*Propylidene Cytidine.*—2′ : 3′-*iso*Propylidene cytidine (1·75 g.; dried for 12 hours at 78°/0·1 mm.; Michelson and Todd, *J.*, 1949, 2476) was dissolved in dry pyridine (50 c.c.), and the solution cooled in ice. Toluene-*p*-sulphonyl chloride (1·18 g., 1 equiv.) was added, and the solution agitated until homogeneous and then left at room temperature overnight, whereupon a partly crystalline sludge separated; to this, water (10 c.c.) was added, followed by ice-cold saturated sodium hydrogen carbonate solution (100 c.c.). After effervescence ceased, the solution was extracted with ice-cold chloroform (3 × 100 c.c.), and the extract washed with ice-cold saturated sodium hydrogen sulphate solution (2 × 200 c.c.) and then with ice-water (2 × 200 c.c.). Solvents were removed under reduced pressure at room temperature, leaving a colourless resin which was dissolved in chloroform (40 c.c.); light petroleum (b. p. 60—80°) was then added to opalescence. During 36 hours at 0° a colourless oil separated. The supernatant liquid was decanted, the oil washed with light petroleum, and the flask evacuated, giving the product as a cream-coloured foam (0·146 g.), which decomposed slowly and indefinitely between 205° and 224° (Found, in material dried at 78°/15 mm. for 6 hours: C, 52·4; H, 5·2; N, 9·5. Calc. for $C_{19}H_{23}O_7N_3S$: C, 53·3; H, 5·3; N, 9·6%).

Paper chromatography (Whatman No. 1) with ethanol–ammonia–water (80 : 4 : 16) resolved the product into two pyrimidine components, detected by photography in ultra-violet light, having R_P values of 0·85 and 0·61. No free toluene-*p*-sulphonic acid was detectable and it is presumed that the product was a mixture of 5′-toluene-*p*-sulphonyl and *N*-toluene-*p*-sulphonyl compounds. This product (137 mg.) was dissolved in dry acetone (20 c.c.) and heated in a sealed tube at 100° for 45 minutes. Within a few minutes a colourless fibrous solid separated. The solid (83 mg.) was filtered off and washed with dry acetone. This product, 2′ : 3′-iso*propylidene* O^2 : 5′-cyclo*cytidine toluene*-p-*sulphonate*, was extremely soluble in water; recrystallised from ethanol–acetone it formed long flat prisms, m. p. 242° (decomp.) (Found, in material dried at 78°/15 mm. for 6 hours: C, 52·3; H, 5·4; N, 9·2. $C_{19}H_{23}O_7N_3S$ requires C, 52·2; H, 5·3; N, 9·6%).

The supernatant mother-liquors of the mixture of covalent toluene-*p*-sulphonyl compounds, when kept at room temperature for 24 hours, deposited a water-soluble solid (713 mg.), m. p. 140° (decomp.) undepressed on admixture with the product of rearrangement in acetone solution.

Paper chromatography (Whatman No. 1) of the crystalline rearrangement product with ethanol–ammonia–water (80 : 4 : 16) gave a large diffuse pyrimidine spot (R_P = 0·71), detected by photography in ultra-violet light, together with an acidic spot (R_P = 0·77) corresponding to the anion of toluene-*p*-sulphonic acid, detected as above. In *tert.*-butanol–ammonia–water (80 : 4 : 16) the pyrimidine moiety was resolved, with trailing into two spots having R_P = 0·74 and 0·42 respectively. From these observations it was apparent that the *cyclo*cytidine product underwent some decomposition in the presence of weak bases.

Ebullioscopic determination, in ethanol, of the molecular weight of the crystalline rearrangement product gave a value of 205 ($C_{19}H_{23}O_7N_3S$ requires *M*, 437); hence the Van't Hoff factor is 2, as required by a uni-univalent ionic species.

Acid Hydrolysis of 2′:3′-isoPropylidene O^2 *:5′-cycloCytidine Toluene-p-sulphonate.*—2′:3′-*iso*-Propylidene O^2 :5′-*cyclo*cytidine toluene-*p*-sulphonate (24·6 mg.) was dissolved in water (1 c.c.) and sulphuric acid added (1 c.c.; N.). The clear solution was heated on the steam-bath for 2 hours and ethanol (10 c.c.) added. The solution was evaporated to a small bulk (1 c.c.), and acetone (5 c.c.) added. When the mixture was kept at 0° overnight, colourless needle-like prisms separated (10·3 mg.). These were collected and washed with acetone; they had m. p. 218—219° (Kofler block), undepressed on admixture with an authentic specimen of cytidine sulphate.

Paper chromatography (Whatman No. 1) of the hydrolysis product with *tert.*-butanol–ammonia–water (80 : 4 : 16) confirmed its homogeneity and established the presence of sulphate ion and cytidine (R_F = 0·25; reference cytidine spot, R_F = 0·25).

We record our indebtedness to Dr. R. N. Haszeldine for some of the absorption spectra, to Mr. F. C. Baker for molecular-weight determinations, and to Dr. J. Davoll for some of the initial work on adenosine. Grateful acknowledgment is made to the Department of Scientific and Industrial Research for a Maintenance Allowance (to J. Z.) and to Roche Products Ltd. for grants and gifts of material.

UNIVERSITY CHEMICAL LABORATORY AND CAVENDISH LABORATORY,
CAMBRIDGE. [*Received, May 21st* 1951.]

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656. *Adsorption from Binary Solutions of Completely Miscible Liquids. Part I. Calculation of Surface Mole-fraction Isotherms.*

By G. A. H. ELTON.

It is shown that for adsorption by a solid from a solution of two completely miscible liquids, individual adsorption isotherms for the two components can be calculated from isotherms of apparent adsorption (concentration change), provided that allowance is made for the fact that adsorption of one component must always be accompanied by desorption of the other. The method is applied to Innes and Rowley's data on adsorption from methanol–carbon tetrachloride mixtures by charcoal, giving results in reasonably good agreement with those previously obtained by thermodynamic calculations based on vapour adsorptions.

WHEN a binary solution is shaken with a solid adsorbent, one of the components may be preferentially adsorbed, bringing about a decrease in the mole-fraction of this component in the solution. For a solution comprising two completely miscible liquids, A and B, experiments of this kind can be carried out over the complete mole-fraction range. If component B is preferentially adsorbed, the excess of B present in the surface layer is usually calculated as $-(n_A + n_B)\Delta x_B$ (see, *e.g.*, Bartell and Sloan, *J. Amer. Chem. Soc.*, 1929, **51**, 1643), where n_A, n_B are the total number of moles of A and B, respectively, in the system, and Δx_B is the increase of mole-fraction of B in the solution. When $-(n_A + n_B)\Delta x_B$ is plotted as a function of x_B, isotherms of two types may be obtained, as shown in Figs. 1 and 2. In each case the adsorption is zero at the two extremes of mole-fraction, as is to be expected, but zero adsorption is sometimes also found at an intermediate mole-fraction, where the adsorption changes sign.

In order to interpret isotherms of the two kinds, it has been suggested (see, *e.g.*, Bartell and Sloan, *loc. cit.*; Ostwald and de Izaguirre, *Kolloid-Z.*, 1922, **30**, 279; Kipling, *Quart. Reviews*, 1951, V, 60) that simultaneous adsorption of both components occurs, the adsorption of each component following independently a Freundlich- or Langmuir-type isotherm of the type encountered in gas adsorption. Depending on the relative magnitudes of the adsorption of the two components, the net apparent adsorption of one of them, as measured by the concentration change, could be positive, negative, or zero. By using suitable empirical constants in two simultaneous Freundlich isotherms, experimental curves of both types can be reproduced (Kipling, *loc. cit.*).

Various objections to this method can be made. Adsorption from the liquid phase differs greatly from adsorption from the gas phase in that in the former case the solid is always covered with a layer of molecules of A and B, even in the absence of adsorption. One or more of these layers may be firmly bound to the adsorbent by a molecular force field, giving a surface zone in which the mole-fraction may differ from the bulk mole-fraction. If the zone is of constant thickness, extra molecules of B can be incorporated into it only at the expense of displacing some molecules of A, and the adsorption of A can only be independent of the adsorption of B if the surface zone is of continually varying thickness, which is not generally considered to be the case. In fact most available evidence indicates that such surface zones are of unimolecular

thickness, except where the preferentially adsorbed component is of low solubility in the second component (McBain and Swain, *Proc. Roy. Soc.*, 1936, *A*, **154**, 608; Guggenheim and Adam, *ibid.*, 1933, *A*, 139, 218; Hansen, Fu, and Bartell, *J. Physical Chem.*, 1949, **53**, 769; Fu and Bartell, *ibid.*, 1950, **54**, 537). Hence the decrease in mole-fraction of the preferentially adsorbed component is due to two factors: first, the decrease in the number of its molecules

FIG. 1.

Apparent adsorption of benzene (B) *from ethyl carbonate by charcoal* (*Bartell and Sloan*).

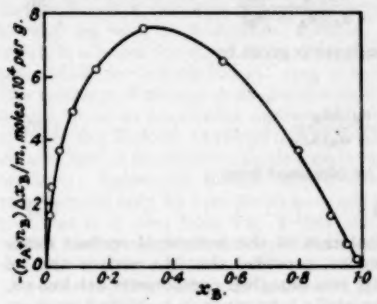
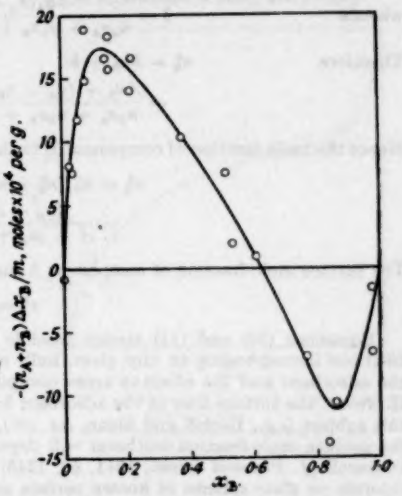


FIG. 2.

Apparent adsorption of carbon tetrachloride (B) *from methanol by charcoal* (*Innes and Rowley*).



present in the bulk solution, and secondly, the increase in the number of molecules of the second component in the bulk solution.

In many practical adsorption experiments, the change in concentration produced by the adsorption is of principal importance, but from a theoretical point of view, a knowledge of the actual composition of the adsorbed layer is desirable, in order that the forces producing the adsorption, and the relative attraction of the adsorbent for the two components, can be assessed.

For a unimolecular surface layer, we have

$$n^s_A a_A + n^s_B a_B = A \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where n^s_A, n^s_B are the number of moles of components A and B respectively in the surface layer, a_A and a_B the corresponding effective areas occupied per mole, and A is the area of adsorbent available. In a solution containing in all n_A moles of A and n_B moles of B, the surface layer would, in the absence of adsorption, contain kn_A and kn_B moles respectively where

$$k(n_A a_A + n_B a_B) = A \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

In a similar solution where the surface layer contains an excess δ moles of component B, there will be a deficiency $\delta a_B/a_A$ moles of component A in the layer, these having been displaced by the excess of component B. Thus equation (1) becomes

$$(kn_A - \delta a_B/a_A) + (kn_B + \delta) = A \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Hence from an initial mole-fraction

$$x^s_B = n_B/(n_A + n_B) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

an equilibrium mole-fraction x_B in the bulk solution is obtained where

$$x_B = \frac{n_B - n^s_B}{(n_A + n_B) - (n^s_A + n^s_B)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Then, from equations (1) and (5)

$$x_B = \frac{a_A\{n_B(1-k)-\delta\}}{a_A(n_A+n_B)(1-k)+\delta(a_B-a_A)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

If the mole-fraction of the solution is measured before and after adsorption, we obtain

$$\Delta x_B = x_B - x_B^0 = \frac{-\delta(n_Aa_A+n_Ba_B)}{(n_A+n_B)\{a_A(n_A+n_B)(1-k)+\delta(a_B-a_A)\}} \quad . \quad . \quad . \quad (7)$$

whence

$$\delta = \frac{-a_A(n_A+n_B)^2(1-k)\Delta x_B}{n_Aa_A+n_Ba_B+\Delta x_B(a_B-a_A)(n_A+n_B)} \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Therefore

$$n_B^s = kn_B+\delta$$

$$= \frac{An_B+(n_A+n_B)\Delta x_B\{A-a_A(n_A+n_B)\}}{n_Aa_A+n_Ba_B+\Delta x_B(a_B-a_A)(n_A+n_B)} \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Hence the mole-fraction of component B in the surface layer is given by

$$x_B^s = n_B^s/(n_A^s+n_B^s)$$

$$= \frac{Ax_B-a_A(n_A+n_B)\Delta x_B}{A+(n_A+n_B)(a_B-a_A)\Delta x_B} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

The surface mole-fraction of component A may then be obtained from

$$x_A^s = 1-x_B^s \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

Equations (10) and (11) render possible the calculation of the individual surface mole-fractions corresponding to any given bulk mole-fractions, provided that the surface area of the adsorbent and the effective areas occupied by the two adsorbed components are known. However, the surface area of the adsorbent has not generally been given in published work on this subject (*e.g.*, Bartell and Sloan, *loc. cit.*), and as is seen from equation (10), the shape of the surface mole-fraction isotherm will depend markedly on the value of A. Urbanic and Damerell (*J. Physical Chem.*, 1941, **45**, 1245) studied adsorption of iodine from carbon tetrachloride on glass spheres of known surface area, but only three points, all in dilute solution, were obtained, not sufficient for the calculation of an isotherm. Further work of this kind, over a larger range of concentration, would be of value, but the difficulty lies in obtaining a sufficiently large surface area of spherical particles to produce measurable concentration changes in concentrated solutions. On the other hand, some adsorbents which are of high surface area, such as silica gel, may produce other complications, due to the occurrence of absorption of one or both of the components into the interior of the adsorbent.

Innes and Rowley (*ibid.*, 1947, **51**, 1172) have evaluated individual surface mole-fraction isotherms for the system methanol (A)–carbon tetrachloride (B)–charcoal by means of a thermodynamic calculation based on measurements of adsorption both from binary solution and from the mixed vapours (*ibid.*, p. 1154). It had previously been shown (*idem*, *ibid.*, 1945, **49**, 411) that the amounts of the two components present in the surface layer were related to the surface pressure, or spreading pressure in the layer, by the approximate expression

$$A\left(\frac{\partial F}{\partial \mu_B}\right)_T = -\frac{(n_A^s+n_B^s)(x_B^s-x_B^s)}{x_A^1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

where F is the spreading pressure, μ_B the chemical potential of component B in the solution, and x_A^1, x_B^1 the mole-fractions of components A and B, respectively, in the solution. For any given solution (the partial pressures of the components being p_A and p_B), the spreading pressure F is given by the equation

$$FA/RT = \int_0^{p_A} n_A^s \mathrm{d}\ln p_A + \int_0^{p_B} n_B^s \mathrm{d}\ln p_B \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

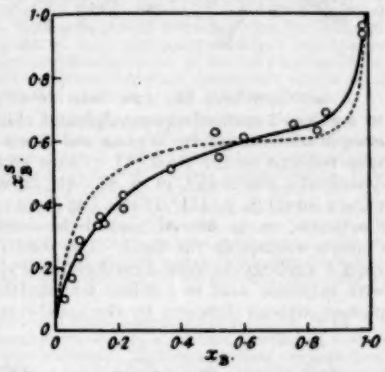
The integrals were evaluated from the areas under graphs of n_A^s against $\ln p_A$ and n_B^s against $\ln p_B$, such graphs being obtained from the data on the adsorption from the vapours. The chemical potential of B as a function of its mole-fraction in the solution was determined from measurements of its partial vapour pressure in solutions of various mole-fractions. The values of $(\partial F/\partial \mu_B)_T$, n_A^s, and n_B^s corresponding to a number of values of x_B^1 were then read off from smoothed curves, and used to calculate the corresponding x_B^s values from equation (12). The

isotherm of apparent adsorption from solution is shown in Fig. 2, and the calculated surface mole-fraction isotherm for component B (carbon tetrachloride) as the dotted line in Fig. 3.

On the other hand, when equation (10) is applied to the data shown in Fig. 2, the only other data required apart from the mole-fraction changes produced by adsorption are the effective areas per mole occupied by A and B in the surface layer, taken by Innes and Rowley as $7{\cdot}66 \times 10^9$ cm.^{2}/mole and $17{\cdot}85 \times 10^9$ cm.^{2}/mole, respectively, and the surface area, obtained from the limiting vapour adsorption as $8{\cdot}3 \times 10^6$ cm.^{2}/g. These values being used, the isotherm of surface mole-fraction of B indicated by the points and the full line in Fig. 3 is obtained directly. The higher degree of scatter shown in the original experimental results (Fig. 2) is due to the fact that the ratio $(n_A + n_B)/m$ was allowed to vary in a random manner, a fact which is allowed for in equation (10), but not in calculating the adsorption as $-(n_A + n_B)\Delta x_B/m$. The isotherm of surface mole-fraction so obtained is seen to be in reasonable agreement with that of Innes and Rowley, the large and varied number of data used in the latters' calculations being borne in mind. Innes and Rowley stated that their results could only be considered as semiquantitative, but it is seen from Fig. 3 that the shapes of the isotherms calculated by the two different methods are very similar. The use of equation (10) in calculating surface mole-fraction isotherms seems much to be preferred in view of the smaller amount of labour involved, and the greater probable accuracy. It is of limited application at present, since, as previously mentioned, sufficient data are rarely available.

FIG. 3.

Surface mole-fraction of carbon tetrachloride (B) in experiments of Innes and Rowley.



○—○ *Calculated for each point from equation* (10).

– – – – – *Smoothed curve obtained by Innes and Rowley using vapour adsorption data.*

It may be stated that, in general, isotherms of apparent adsorption of the type shown in Fig. 2, will correspond to surface-mole-fraction isotherms which, as shown in Fig. 3, cut the line $x^s_B = x_B$ at the mole-fraction corresponding to zero adsorption. The type shown in Fig. 1, will lead to a surface mole fraction isotherm which does not cut the line $x^s_B = x_B$, since $x^s_B > x_B$ at all mole-fractions other than zero and unity. Adsorption of this kind is obtained when the adsorbent has a marked "preference" for one of the components of the solution (see, *e.g.* Kipling, *loc. cit.*).

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657. *A New Synthesis of Lucanthone (Miracil D, Nilodin).**

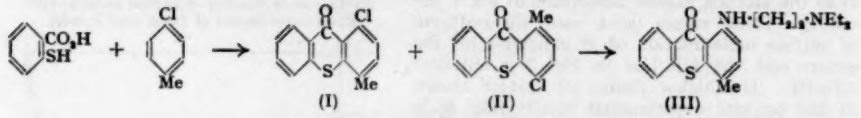
By THOMAS M. SHARP.

A synthesis of lucanthone B.P. (1-2′-diethylaminoethylamino-4-methylthiaxanthone, Miracil D, Nilodin) has been developed which avoids the wasteful production of the non-reactive 4-chloro-1-methylthiaxanthone. Some variants of lucanthone with modified basic side-chains are described.

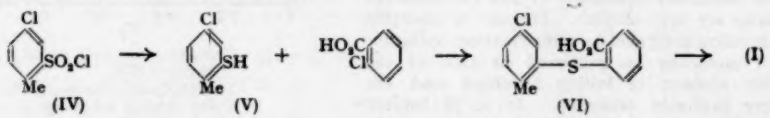
DURING the late war Mauss synthesized a long series of basic-substituted xanthones and thiaxanthones, some of which were found by Kikuth and Gönnert to be effective in the cure of schistosomiasis in experimental animals (*B.I.O.S. Final Report*, No. 116, Item No. 24; *C.I.O.S. Report*, Item No. 24, File No. XXV–54; Mauss, *Chem. Ber.*, 1948, **81**, 19; Kikuth, Gönnert, and Mauss, *Naturwiss.*, 1946, **33**, 253). One of the compounds, 1-2′-diethylaminoethylamino-4-methylthiaxanthone (lucanthone B.P., Miracil D, Nilodin) is now used clinically

* Patents pending.

in the treatment of human schistosomiasis caused by *Schistosoma haematobium*. For the synthesis of lucanthone, Mauss heated 2-diethylaminoethylamine with the inseparable mixture of 1-chloro-4-methyl- (I) and 4-chloro-1-methyl-thiaxanthone (II) which Ullmann and Glenck (*Ber.*, 1916, **49**, 2487) had obtained by the Davis–Smiles condensation (*J.*, 1910, **97**, 1290) of thiosalicylic acid with *p*-chlorotoluene; the labile chlorine atom in (I) was replaced while (II) remained unchanged. The process is simple but the formation of the unreactive isomeride (II) involves the waste of about half the material.



A new synthesis has now been developed in which *p*-chlorotoluene is chlorosulphonated to 5-chloro-2-methylbenzenesulphonyl chloride (IV) (anilide, m. p. 144°), identical with the compound obtained by Wynne and Bruce (*J.*, 1898, **73**, 762) *via* the sulphonic acid; this is then reduced to the thiol (V). Chien and Kuan (*J. Chinese Chem. Soc.*, 1936, **4**, 355) have described a compound, m. p. 80—81°, to which they ascribe structure (V). We find the thiol to be a liquid (b. p. 111°/17 mm.) at room temperature, quantitatively oxidized by iodine to the disulphide, m. p. 80—81°, which is clearly identical with the compound described by the Chinese workers as the thiol. The thiol (V) condenses readily with *o*-chlorobenzoic acid, to yield 2′-carboxy-5-chloro-2-methyldiphenyl sulphide (VI) which readily undergoes ring closure with sulphuric acid to 1-chloro-4-methylthiaxanthone (I). The final stage to (III) is accomplished without difficulty by the usual method.



It is interesting that the melting point of the acid (VI) is the same as that of the isomeric 2′-carboxy-2-chloro-5-methyldiphenyl sulphide obtained by Ullmann and Glenck by an unambiguous route, and that the melting point of 1-chloro-4-methyl- is the same as that of 4-chloro-1-methyl-thiaxanthone (I and II). The melting point of a mixture of the chloromethylthiaxanthones is higher than that of either individual compound, which suggests the formation of a molecular complex and perhaps explains the failure of Ullmann and Glenck to effect a separation of the isomerides by fractional crystallization.

Synthesis of the acid (VI) has also been effected by condensation of the thiol (V) with diazotized anthranilic acid (cf. Ziegler, *Ber.*, 1890, **23**, 2471).

Compounds containing a few variants of the basic side-chain of (III) have been prepared; these were found by Mr. O. D. Standen to be less active in experimental schistosomiasis than lucanthone.

Experimental.

4-Chlorotoluene-2-sulphonyl Chloride (IV) [With M. M. Coombs].—*p*-Chlorotoluene (75 g.) in dry chloroform (375 c.c.) was cooled to 10—12° in absence of moisture and stirred while chlorosulphonic acid (207 g.) was added at such a rate that the temperature did not exceed 20° (15 minutes). Stirring was continued for ½ hour at 25° and a further ½ hour at 50°. After cooling, the product was stirred on to ice (750 g.), the chloroform layer dried (Na_2SO_4), and the solvent removed. The residue was distilled under reduced pressure and the fraction, b. p. 154°/16 mm., m. p. 24°, collected; the yield was 88·7—103 g. (66·6—77·8%) (Found: S, 14·5. Calc. for $C_7H_6O_2SCl_2$: S, 14·2%). The anilide, m. p. 143—145°, is identical with that prepared by Wynne and Bruce (*loc. cit.*).

5-Chloro-2-methylthiophenol (V).—Sulphuric acid (98%; 138 g.) was added to 450 c.c. of ice-water, and molten 4-chlorotoluene-2-sulphonyl chloride (45 g.) added with vigorous stirring. The mixture was cooled rapidly to −10° to −15° and zinc dust (78·5 g.) added in portions, the temperature being kept below −5°. Stirring was continued for 2 hours at room temperature and the mixture was finally heated gently under reflux for a further 2 hours. *5-Chloro-2-methylthiophenol* was isolated by steam-distillation as a heavy colourless oil, b. p. 114—117°/17 mm. (29·9 g., 94·2%) (Found: C, 52·8; H, 4·7; S, 20·2. C_7H_7ClS requires C, 53·1; H, 4·5; S, 20·25%). 0·1558 G. required 9·8 c.c. of 0·1013N-iodine. Oxidation of 2-SH to S–S requires 9·7 c.c.; the oxidation product had m. p. 80—81°.

2′-Carboxy-5-chloro-2-methyldiphenyl Sulphide (IV) [with A. G. Turner].—(*a*) 5-Chloro-2-methylthiophenol (7·9 g.), *o*-chlorobenzoic acid (7·7 g.), anhydrous potassium carbonate (6·92 g.), benzyl

alcohol (80 c.c.), copper powder (0·5 g.), and potassium iodide (1·0 g.) were stirred and heated under reflux for 5 hours. After cooling, the solution was filtered, diluted with ether (300 c.c.), and extracted with 1% aqueous sodium hydroxide. The combined extracts were decolorized with charcoal, filtered hot, and acidified; *2'-carboxy-5-chloro-2-methyldiphenyl sulphide* separated and was filtered off from the hot solution. After crystallization from toluene it formed colourless felted needles, m. p. 195—197° (12·28 g., 87·7%) (Found: C, 60·6; H, 4·0. $C_{14}H_{11}O_2SCl$ requires C, 60·3; H, 4·0%). If a smaller quantity of potassium carbonate is used the product consists largely of the benzyl ester of the above acid.

(*b*) Anthranilic acid (2·74 g.), dissolved in hot sodium hydroxide solution (10%; 8·5 c.c.), was treated with solid sodium nitrite (1·54 g.), and the solution cooled to 5° and added slowly to 2*N*-hydrochloric acid (22 c.c.) at 0°. Excess of nitrous acid was removed with urea, and the cold diazo-solution added to 5-chloro-2-methylthiophenol (3·16 g.) in aqueous ammonia (*d* 0·885; 9·5 c.c.) diluted with an equal volume of water, the temperature being kept below 20°. The yellow solid formed during the addition slowly decomposed with evolution of nitrogen. After about an hour the orange solution was filtered off from a small amount of 5 : 5'-dichloro-2 : 2'-dimethyldiphenyl disulphide (m. p. 80—82°) and acidified. A light brown precipitate of 2'-carboxy-5-chloro-2-methyldiphenyl sulphide separated, which after crystallisation had m. p. 195—197°, identical with that obtained under (*a*). The yield was 50%.

1-Chloro-4-methylthiaxanthone (I).—2'-Carboxy-5-chloro-2-methyldiphenyl sulphide (8·2 g.) in sulphuric acid (98%; 25 c.c.) was heated on a water-bath for 75 minutes. The clear red-brown solution, after cooling, was stirred on to ice (250 g.), and the precipitated *1-chloro-4-methylthiaxanthone* was collected, extracted with dilute ammonia, refiltered, washed, and dried. After crystallisation from alcohol it forms pale yellow needles, m. p. 143—145° (6·92 g., 90·2%) (Found: C, 64·5; H, 3·7. $C_{14}H_9OSCl$ requires C, 64·5; H, 3·5%). Ullmann and Glenck (*loc. cit.*) by distillation and fractional crystallisation of the mixture of 1-chloro-4-methyl- and 4-chloro-1-methyl-thiaxanthone obtained a substance, m. p. 150—150·5°, which they thought to be substantially pure 1-chloro-4-methylthiaxanthone. We now find that a mixture of the 1-chloro-4-methyl- (obtained above) and 4-chloro-1-methyl-thiaxanthone (obtained by treatment of Ullmann and Glenck's mixture with 2-diethylaminoethylamine as the non-reactive component) melts at 150°.

1-2'-Diethylaminoethylamino-4-methylthiaxanthone (III).—1-Chloro-4-methylthiaxanthone (6·92 g.), treated by Mauss's method (*loc. cit.*) with 2-diethylaminoethylamine gave a product completely soluble in dilute acetic acid, from which 8·45 g. of crude base were obtained. It formed yellow crystals from alcohol, m. p. 64—65°, and gave a hydrochloride, fine yellow needles, m. p. 196—197° in agreement with the constants recorded by Mauss. The *salicylate* forms stout prisms (from alcohol), m. p. 100—103° (Found: S, 6·7. $C_{20}H_{24}ON_2S,C_7H_6O_3$ requires S, 6·85%). The *methylenebishydroxynaphthoate* has no characteristic sharp m. p.; it decomposes from about 120° onwards (Found: C, 70·7; H, 5·8; S, 5·75. $C_{20}H_{24}ON_2S,\frac{1}{2}C_{23}H_{16}O_6$ requires C, 70·4; H, 6·0; S, 6·0%). The *methiodide*, orange needles from methanol, has m. p. 237° (decomp.) (Found: C, 52·3; H, 5·3; I, 26·2, 26·4. $C_{20}H_{24}ON_2S,CH_3I$ requires C, 52·3; H, 5·4; I, 25·2%). The *ethiodide* forms fine orange needles (from water), m. p. 210° (decomp.) (Found: C, 52·9; H, 5·4; I, 25·2. $C_{20}H_{24}ON_2S,C_2H_5I$ requires C, 53·2; H, 5·9; I, 25·6%).

1-2'-Dimethylaminoethylamino-4-methylthiaxanthone.—The *hydrochloride*, prepared in a similar manner from 1-chloro-4-methylthiaxanthone and 2-dimethylaminoethylamine, forms yellowish-orange needles (from alcohol), m. p. 233—235° (Found: C, 61·9; H, 5·85; S, 9·0; Cl, 10·2. $C_{18}H_{20}ON_2S,HCl$ requires C, 62·0; H, 6·1; S, 9·2; Cl, 10·2%).

1-2'-Di-n-butylaminoethylamino-4-methylthiaxanthone.—The *hydrochloride* from 1-chloro-4-methylthiaxanthone and 2-di-*n*-butylaminoethylamine (Bloom, Breslow, and Hauser, *J. Amer. Chem Soc.*, 1945, **67**, 539) forms golden needles, m. p. 167—169° (Found: C, 66·7; H, 8·1; S, 7·25. $C_{24}H_{32}ON_2S,HCl$ requires C, 66·7; H, 7·7; S, 7·4%).

4-Methyl-1-2'-pyrrolidinoethylaminothiaxanthone.—The *hydrochloride* from 1-chloro-4-methylthiaxanthone and 2-pyrrolidinoethylamine (van Alphen, *Rec. Trav. chim.*, 1939, **58**, 1105) forms small orange needles (from alcohol), m. p. 241—243° (Found: Cl, 9·4; S, 8·3. $C_{20}H_{22}ON_2S,HCl$ requires Cl, 9·5; S, 8·55%).

1-4'-Ethylpiperazino-4-methylthiaxanthone.—The *hydrochloride* from 1-chloro-4-methylthiaxanthone and 1-ethylpiperazine (Moore, Boyle, and Thorn, *J.*, 1929, 47) forms yellow prismatic needles (from alcohol), m. p. 297° (decomp.) (Found: Cl, 9·6; S, 8·3. $C_{20}H_{21}ON_2S,HCl$ requires Cl, 9·5; S, 8·55%).

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THE WELLCOME LABORATORIES OF TROPICAL MEDICINE,
LONDON, N.W.1.

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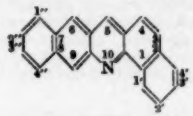
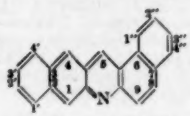
658. *Carcinogenic Nitrogen Compounds. Part IX.* The Use of Aminotetralins for the Synthesis of Dibenzacridines and Related Compounds.*

By Ng. Ph. Buu-Hoï and Pierre Jacquignon.

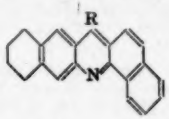
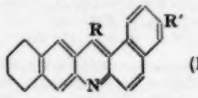
The use is described of 5 : 6 : 7 : 8-tetrahydro-2-naphthylamine for the synthesis of some 1 : 2-7 : 8- and 3 : 4-7 : 8-dibenzacridines; 3-ethyl-5 : 6 : 7 : 8-tetrahydro-2-naphthylamine has similarly been applied to the preparation of 9-ethyl-1 : 2-6 : 7- and 1-ethyl-3 : 4-6 : 7-dibenzacridine. In addition to these acridines, various other polycyclic nitrogenous compounds have been prepared for biological investigation.

1 : 2-6 : 7- and 3 : 4-6 : 7-Dibenzacridine have repeatedly been found carcinogenic both on skin painting and on subcutaneous injection (Barry, Cook, Haslewood, Hewett, and Kennaway, *Proc. Roy. Soc.*, 1935, *B*, **117**, 318; Badger, Cook, Hewett, Kennaway, Martin, and Robinson, *ibid.*, 1940, *B*, **129**, 439; Rondoni and Corbellini, *Tumori*, 1936, **10**, 106). Some homologues of these two dibenzacridines are similarly active (Lacassagne, Buu-Hoï, Lecocq, and Rudali, *Bull. Cancer*, 1946, **33**, 48), and 1 : 2-8 : 9-dibenzacridine is now under test in this Institute. It was also deemed of interest to investigate the activity of the two remaining angular dibenzacridines,

(I)   (II)

the 1 : 2-7 : 8- and the 2 : 3-6 : 7- isomers (I) and (II). Of these two aza-derivatives of 1 : 2-benzotetracene, the former was unknown, and the latter had been prepared by Strohbach (*Ber.*, 1901, **34**, 3157) by distillation of the corresponding acridone with zinc.

We have now found that 5 : 6 : 7 : 8-tetrahydro-2-naphthylamine readily underwent Ullmann–Fetvadjian reactions (*Ber.*, 1903, **36**, 1029) with paraformaldehyde and both α- and β-naphthol, to give 1″ : 2″ : 3″ : 4″-tetrahydro-1 : 2-7 : 8- (III; R = H) and 1′ : 2′ : 3′ : 4′-tetrahydro-2 : 3-6 : 7-dibenzacridine (IV; R = R′ = H) respectively; 6-*tert.*-butyl-2-naphthol led to 2″-*tert.*-butyl-1′ : 2′ : 3′ : 4′-tetrahydro-2 : 3-6 : 7-dibenzacridine (IV; R = H, R′ = Bu^t). Dehydrogenation of the first two compounds to 1 : 2-7 : 8- and 2 : 3-6 : 7-dibenzacridine was

(III)   (IV)

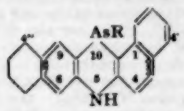
successfully effected with selenium; this showed the high degree of stability of the acridine nucleus, for in most of the reported cases of selenium dehydrogenation of nitrogen-containing heterocyclic compounds, widespread destruction of the molecular structure ensued (see, for instance, Rössner, *Z. physiol. Chem.*, 1937, **249**, 267). Had the Ullmann–Fetvadjian reactions with 5 : 6 : 7 : 8-tetrahydro-2-naphthylamine taken an angular course, the known 1 : 2-6 : 7- and 2 : 3-5 : 6-dibenzacridines would have been obtained. The linear cyclisation is parallel to the preferential formation of 6 : 7-*cyclo*hexenoquinoline in the Skraup reaction (von Braun and Gruber, *Ber.*, 1922, **55**, 1713), and to the Friedel–Crafts chloroacetylation of aceto-5 : 6 : 7 : 8-tetrahydro-2-naphthalide which occurred at position 7 (Schofield, Swain, and Theobald, *J.*, 1949, 2399).

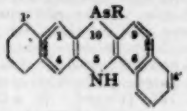
5 : 6 : 7 : 8-Tetrahydro-2-naphthylamine readily gave Knoevenagel reactions with α- and β-naphthol in the presence of iodine, giving *N*-(5 : 6 : 7 : 8-tetrahydro-2-naphthyl)-α- and β-naphthylamine respectively. These secondary amines underwent modified Bernthsen reactions (see Buu-Hoï, *J.*, 1950, 1146) with acetic anhydride, to yield (III; R = Me) and (IV; R = Me, R′ = H), and similar compounds were obtained with propionic anhydride. These substances could be considered as belonging to the trialkyl-1 : 2- and -3 : 4-benzacridine class, in which many carcinogenic representatives have already been found (Zajdela and Buu-Hoï, *Acta Unio Intern. contra Cancrum*, 1950, **7**, 184).

The ability of certain polycyclic arsines to give transient tumours on skin painting (Visser and

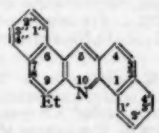
* Part VIII, *J.*, 1951, 2871.

ten Seldam, *Geneesk. Tijdschr. Nederl.-Indië*, 1938, **78**, 3280; Buu-Hoï and Royer, *J.*, 1951, 795) led us to synthesise 10-chloro-5 : 10 : 1″ : 2″ : 3″ : 4″-hexahydro-1 : 2-7 : 8- (V; R = Cl) and -5 : 10 : 1′ : 2′ : 3′ : 4′-hexahydro-2 : 3-6 : 7-dibenzophenarsazine (VI; R = Cl) from arsenic trichloride and the two above-mentioned *N*-tetralylnaphthylamines in the usual way (Burton and Gibson, *J.*, 1926, 2243; Buu-Hoï and Royer, *loc. cit.*). The action of methyl- and ethyl-magnesium iodides on these orange-yellow, sternutatory chloroarsines led to the corresponding colourless, non-irritant 10-alkyl-5 : 10 : 1″ : 2″ : 3″ : 4″-hexahydro-1 : 2-7 : 8- (V; R = Me or Et) and -5 : 10 : 1′ : 2′ : 3′ : 4′-hexahydro-2 : 3-6 : 7-dibenzophenarsazines (VI; R = Me or Et).

(V) 

 (VI)

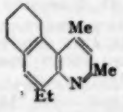
The 5 : 6 : 7 : 8-tetrahydro-2-naphthylamine used in this work was conveniently prepared from tetralin by Friedel–Crafts acetylation, and Beckmann rearrangement of 6-acetyltetralin oxime. It was found that a similar sequence of reactions, starting from 7-ethyltetralin, readily yielded 3-ethyl-5 : 6 : 7 : 8-tetrahydro-2-naphthylamine *via* 6-acetyl-7-ethyltetralin. The fact that Friedel–Crafts acetylation of 7-ethyltetralin involved position 6 and not position 8 was proved by the ability of the parent amine to undergo cyclisation reactions, and is also in accord with similar cases reported in the literature (Fleischer and Siefert, *Ber.*, 1920, **53**, 1259; Schroeter, *Annalen*, 1922, **426**, 66). 3-Ethyl-5 : 6 : 7 : 8-tetrahydro-2-naphthylamine was found a convenient intermediate for the synthesis of homologues of the bisangular 1 : 2-6 : 7- and 3 : 4-6 : 7-dibenzacridine. The Ullmann–Fetvadjian reaction with α- and β-naphthol gave 9-ethyl-1″ : 2″ : 3″ : 4″-tetrahydro-1 : 2-6 : 7- and 1-ethyl-1′ : 2′ : 3′ : 4′-tetrahydro-3 : 4-6 : 7-dibenzacridine respectively; dehydrogenation of these to 9-ethyl-1 : 2-6 : 7- (VII) and 1-ethyl-3 : 4-

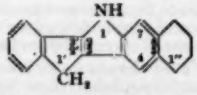
(VII) 

(VIII)

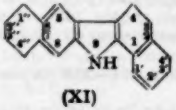
6 : 7-dibenzacridine (VIII) could, surprisingly, be effected by selenium without the loss of the ethyl group, which in both instances is linked to a "*meso*-phenanthrene" carbon atom. It was previously known that alkyl groups located on regions of high π-electron density are easily removed in high-temperature reactions (see, *e.g.*, Fieser, "Organic Reactions," 1942, Vol. I, 129).

Several other nitrogenous heterocyclic compounds were prepared from 5 : 6 : 7 : 8-tetrahydro-2-naphthylamine and its 3-ethyl derivative, for biological testing. Knorr–Paal condensation (Knorr, *Ber.*, 1885, **18**, 2254) with acetonylacetone gave 2 : 5-dimethyl-1-2′-tetralylpyrroles. Combes's reaction (*Compt. rend.*, 1886, **106**, 1536) between acetylacetone and the ethyl-amine yielded (IX); 5 : 6 : 7 : 8-tetrahydro-2-naphthylamine gave a liquid product,

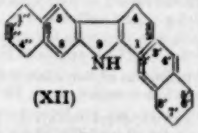
(IX) 

 (X)

probably a mixture of the two possible isomers (cf. Lindner, Djulgerowa, and Mayer, *Monatsh.*, 1923, **44**, 340). Finally, it was found that 5 : 6 : 7 : 8-tetrahydro-2-naphthylhydrazones of cyclic ketones readily underwent Fischer–Borsche cyclisation; from indan-1-one was thus



(XI)



(XII)

obtained 1″ : 2″ : 3″ : 4″-tetrahydro-5 : 6-benzindeno(3′ : 2′-2 : 3)indole (X); from 1-tetralone, 3 : 4 : 1″ : 2″ : 3″ : 4″-hexahydro-1 : 2-6 : 7-dibenzocarbazole (XI); and from 1-keto-

1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydroanthracene (Kroffpfeiffer and Schäfer, *Ber.*, 1923, **56**, 620), 3 : 4 : 5′ : 6′ : 7′ : 8′ : 1″ : 2″ : 3″ : 4″-decahydro-6 - 7-benzonaphtho(2′ : 3′-1 : 2)carbazole (XII). There was no rigid proof here for linear cyclisation, but this was made probable by the high melting points of the products and by the evidence given above for the acridine cyclisations.

Experimental.

Preparation of 5 : 6 : 7 : 8-*Tetrahydro-2-naphthylamine*.—6-Acetyltetralin (220 g. ; b. p. 180°/19 mm.) was obtained from tetralin (270 g.), acetyl chloride (165 g.), and aluminium chloride (325 g.) in carbon disulphide in the usual way, the reaction mixture being kept at room temperature for only 6 hours to avoid side-condensations. Beckmann rearrangement of 6-acetyltetralin oxime (85 g. ; m. p. 106°) was performed (at variance with the MacLeish and Campbell, *J.*, 1937, 1107; see also Schofield, Swain, and Theobald, *loc. cit.*) with phosphorus pentachloride (112 g.) at 0° in anhydrous ether. The reaction was instantaneous and gave a 98% yield of aceto-5 : 6 : 7 : 8-tetrahydro-2-naphthalide, b. p. 244°/19 mm., m. p. 106°. The *toluene*-p-*sulphonyl* derivative of the free amine, prepared in pyridine, formed from ethanol large leaflets, m. p. 137° (Found : N, 4·5. $C_{17}H_{19}O_3NS$ requires N, 4·6%); the N-*acetylsulphanilyl* derivative, similarly prepared, formed from ethanol shiny needles, m. p. 216° (Found : N, 8·1. $C_{18}H_{20}O_3N_2S$ requires N, 8·1%).

6-*Acetyl*-7-*ethyltetralin*.—6-Ethyltetralin (70 g. ; b. p. 239°) prepared from 6-acetyltetralin (100 g.) (cf. Huang-Minlon, *loc. cit.*). It (100 g.) was acetylated with acetyl chloride (50 g.) and aluminium chloride (100 g.) in carbon disulphide, as for tetralin ; the *ketone* was a pale yellow oil, b. p. 188°/17 mm. (Found : C, 83·0; H, 9·1. $C_{14}H_{18}O$ requires C, 83·1; H, 8·9%). The *semicarbazone* formed silky needles, m. p. 134—135°, from ethanol (Found : C, 69·1; H, 8·0. $C_{15}H_{21}ON_3$ requires C, 69·5; H, 8·1%), the *thiosemicarbazone* microscopic needles, m. p. 123°, from methanol (Found : C, 65·8; H, 7·8. $C_{15}H_{21}N_3S$ requires C, 65·5; H, 7·6%), and the *oxime* fine needles, m. p. 128°, from methanol (Found : N, 6·2. $C_{14}H_{19}ON$ requires N, 6·4%).

3-*Ethyl*-5 : 6 : 7 : 8-*tetrahydro-2-naphthylamine*.—Beckmann rearrangement of the foregoing oxime (33 g.) by means of phosphorus pentachloride (30 g.) in ether (80 c.c.) gave *acet*-3-*ethyl*-5 : 6 : 7 : 8-*tetrahydro-2-naphthalide* (32·5 g.), crystallising from ethanol in fine needles, m. p. 166° (Found : N, 6·3. $C_{14}H_{19}ON$ requires N, 6·4%). A suspension of this amide (32 g.) in hydrochloric acid (100 c.c.) was refluxed for 30 minutes ; after cooling, the solid amine hydrochloride (m. p. 147° after recrystallisation from water) gave on basification the free *amine* (20 g.) as a pale yellow viscous oil, b. p. 175°/16 mm. (Found : C, 82·3; H, 9·9. $C_{12}H_{17}N$ requires C, 82·3; H, 9·7%). Its *toluene*-p-*sulphonyl* derivative formed leaflets, m. p. 130°, from ethanol (Found : N, 4·3. $C_{19}H_{23}O_2NS$ requires N, 4·4%). Its *N*-acetylsulphanilyl derivative formed shiny needles, m. p. 201°.

1″ : 2″ : 3″ : 4″-*Tetrahydro*-1 : 2-7 : 8-*dibenzacridine* (III ; R = H).—To a boiling mixture of 5 : 6 : 7 : 8-tetrahydro-2-naphthylamine (5 g.) and α-naphthol (5 g.), paraformaldehyde (0·75 g.) was added in small portions ; the reaction mixture was subsequently boiled for some minutes and then fractionated in a vacuum. The portion boiling at 340—345°/18 mm. (2 g.) gave, after repeated crystallisation from a mixture of ethanol and benzene, fine pale yellow needles, m. p. 118° (Found : C, 88·8; H, 6·1. $C_{21}H_{17}N$ requires C, 89·0% H, 6·0%). The picrate formed from nitrobenzene shiny orange-red prisms, m. p. 257° (decomp. >232°).

1 : 2-7 : 8-*Dibenzacridine* (I).—The foregoing tetrahydro-compound (0·5 g.) was heated with selenium powder (0·3 g.) at 350° for 3 hours. After cooling, the reaction product was extracted several times with ethanol ; the residue (0·4 g.) left on evaporation gave, on repeated recrystallisation from ethanol, fine pale yellow needles, m. p. 129° (Found : C, 89·7; H, 4·6. $C_{21}H_{13}N$ requires C, 90·0; H, 4·6%). The picrate formed from nitrobenzene brick-red needles, m. p. 266° (decomp. >242°).

1′ : 2′ : 3′ : 4′-*Tetrahydro*-2 : 3-6 : 7-*dibenzacridine* (IV; R = R′ = H).—Obtained similarly from β-naphthol, the portion of the product boiling at 340—345°/17 mm. (4 g.) gave, after repeated recrystallisation from ethanol and benzene, fine pale yellow prisms, m. p. 145°, giving with sulphuric acid a deep yellow colour as did the isomer (III) (Found : C, 88·6; H, 6·0. $C_{21}H_{17}N$ requires C, 89·0; H, 6·0%).

2 : 3-5 : 7-*Dibenzacridine* (II).—Formed from ethanol in fine yellow prisms, m. p. 209° (lit., m. p. 206°), this gave with sulphuric acid a vermilion colour (Found : C, 89·7; H, 4·6. Calc. for $C_{21}H_{13}N$: C, 90·0; H, 4·6%). The picrate formed orange-red needles, m. p. 295° (decomp. >266°), from nitrobenzene.

3′-tert.-*Butyl*-1′ : 2′ : 3′ : 4′-*tetrahydro*-2 : 3-6 : 7-*dibenzacridine*.—Obtained in the usual way from the amine (2 g.), 6-*tert.*-butyl-2-naphthol (Buu-Hoï *et al.*, *J. Org. Chem.*, 1950, **15**, 1060) (2·2 g.), and paraformaldehyde (0·5 g.), the portion of the product boiling at 350—355°/17 mm. (3 g.) was transformed into a picrate which crystallised from benzene in fine shiny orange needles, decomposing at >231—232°. Treatment with aqueous ammonia gave the free *acridine* which formed pale yellow needles, m. p. 128°, from ethanol (Found : C, 88·2; H, 7·3. $C_{25}H_{25}N$ requires C, 88·6; H, 7·4%).

N-(5 : 6 : 7 : 8-*Tetrahydro-2-naphthyl*)-α-*naphthylamine*.—α-Naphthol (12·5 g.), 5 : 6 : 7 : 8-tetrahydro-2-naphthylamine (7·5 g.), and iodine (0·1 g.) were heated for 5 hours at 240—245°. The reaction mixture gave, on fractionation in a vacuum, the secondary *amine* as a yellow viscous oil (12 g.) b. p. 285—290°/16 mm. (Found : N, 5·0. $C_{20}H_{19}N$ requires N, 5·1%).

The β-*isomer*, obtained as above from β-naphthol (25 g.), had b. p. 304—305°/16 mm., and crystallised from ethanol in colourless needles, m. p. 98° (Found : N, 4·9%).

1″ : 2″ : 3″ : 4″-*Tetrahydro*-5-*methyl*-1 : 2-7 : 8-*dibenzacridine* (III ; R = Me).—The foregoing secondary α-amine (2 g.), acetic anhydride (2 g.), and fused zinc chloride (2 g.) was heated at 180—190° for 6 hours ; the product was treated with hot aqueous sodium hydroxide, and the *acridine* taken up in toluene. The toluene solution was dried (Na_2SO_4), the solvent removed, and the residue distilled in a vacuum.

The portion boiling at 340—350°/16 mm. (1·5 g.) was transformed into a picrate, crystallising from toluene in orange-yellow needles, m.p. 251°. Decomposition of the picrate with ammonia yielded the free *base* which formed pale yellow prisms, m. p. 130°, from ethanol (Found : C, 88·4; H, 6·3. $C_{23}H_{19}N$ requires C, 88·8; H, 6·4%).

5-*Ethyl*-1'' : 2'' : 3'' : 4''-*tetrahydro*-1 : 2-7 : 8-*dibenzacridine* (III; R = Et).—Similarly obtained with propionic anhydride (2 g.), this compound formed an orange-yellow picrate (from toluene), m. p. 223° (decomp. at >200°); the free *acridine* crystallised from ethanol in yellowish silky needles, m. p. 114° (Found : C, 88·4; H, 6·6. $C_{23}H_{21}N$ requires C, 88·7; H, 6·7%).

1' : 2' : 3' : 4'-*Tetrahydro*-5-*methyl*-2 : 3-6 : 7-*dibenzacridine* (IV; R = Me, R' = H).—The reactants were *N*-5 : 6 : 7 : 8-tetrahydro-2-naphthyl-β-naphthylamine (5 g.), acetic anhydride (5 g.), and zinc chloride (5 g.); the portion of the product boiling at 335—360°/16 mm. (3 g.) gave a picrate crystallising from nitrobenzene in fine brownish-red prisms, m. p. 272—273° (decomp. at >240°); the free *acridine* formed fine pale yellow prisms, m. p. 166°, from ethanol (Found : C, 88·4; H, 6·2%). The 5-*ethyl* homologue (IV; R = Et, R' = H) gave a picrate, shiny brick-red leaflets (from nitrobenzene), m. p. 253° (decomp. at >236—240°), and crystallised from ethanol in pale yellow needles, m. p. 171° (Found : C, 88·5; H, 6·5%).

10-*Chloro*-5 : 10 : 1' : 2' : 3' : 4'-*hexahydro*-2 : 3-6 : 7-*dibenzophenarsazine* (VI; R = Cl).—A solution of *N*-5 : 6 : 7 : 8-tetrahydro-2-naphthyl-α-naphthylamine (4 g.) and arsenic trichloride (2 g.) in *o*-dichlorobenzene (20 c.c.) was gently refluxed for 2 hours. After cooling, the precipitated *chlorophenarsazine* (3·7 g.) was collected and washed with benzene; it crystallised from toluene in orange-yellow needles, m. p. 264° (decomp. at >256°), giving with sulphuric acid a blood-red colour (Found : C, 62·5; H, 4·2. $C_{23}H_{17}NClAs$ requires C, 62·9; H, 4·4%).

5 : 10 : 1' : 2' : 3' : 4'-*Hexahydro*-10-*methyl*-2 : 3-6 : 7-*dibenzophenarsazine* (VI; R = Me).—The foregoing chloro-compound (0·5 g.) was added in small portions to an ethereal solution of a Grignard reagent (from methyl iodide, 0·5 g.). After 15 minutes' refluxing on a water-bath, the reaction mixture was treated with an ice-cooled aqueous ammonium chloride, and the ethereal solution washed with water and dried (Na_2SO_4). After evaporation of the solvent, the residue crystallised from methanol, giving fine colourless prisms (0·3 g.), m. p. 226° (Found : C, 69·3; H, 5·4. $C_{21}H_{20}NAs$ requires C, 69·8; H, 5·5%). The 10-*ethyl* homologue (VI; R = Et), similarly prepared with ethylmagnesium iodide, formed from methanol colourless needles, m. p. 157°, giving an orange colour with sulphuric acid (Found : C, 70·0; H, 5·7. $C_{22}H_{22}NAs$ requires C, 70·4; H, 5·8%).

10-*Chloro*-5 : 10 : 1'' : 2'' : 3'' : 4''-*hexahydro*-2 : 3-6 : 7-*dibenzophenarsazine* (V; R = Cl).—Prepared from *N*-(5 : 6 : 7 : 8-tetrahydro-2-naphthyl)-β-naphthylamine (4 g.), as was the isomer, the *chloroarsine* formed fine orange-yellow needles (3·7 g.) (from toluene), m. p. 260° (decomp. at >252°), giving with sulphuric acid a brown-red colour (Found : C, 62·6; H, 4·1%).

5 : 10 : 1'' : 2'' : 3'' : 4''-*Hexahydro*-10-*methyl*-2 : 3-6 : 7-*dibenzophenarsazine* (V; R = Me).—This *methylarsine* formed colourless prisms (0·3 g.), m. p. 200°, from methanol, and gave with sulphuric acid an orange colour (Found : C, 69·2; H, 5·4%). The 10-*ethyl* homologue crystallised from ligroin in fine shiny needles, m. p. 146° (Found : C, 70·0; H, 5·8%).

9-*Ethyl*-1'' : 2'' : 3'' : 4''-*tetrahydro*-1 : 2-6 : 7-*dibenzacridine*.—The portion, b. p. 340—345°/17 mm., of the product obtained from α-naphthol (4 g.), 3-ethyl-5 : 6-7 : 8-tetrahydro-2-naphthylamine (4 g.), and paraformaldehyde (0·75 g.) gave this *acridine* as shiny pale greenish-yellow needles, m. p. 132° (from ethanol) (Found : C, 88·5; H, 6·6. $C_{23}H_{21}N$ requires C, 88·7; H, 6·7%). The picrate formed orange-red needles, m. p. 173°, from toluene; such a low m. p. is characteristic of the picrates of 1 : 2-benzacridines bearing an alkyl substituent at position 9 (cf. Buu-Hoï, *J.*, 1949, 670; 1950, 1146).

9-*Ethyl*-1 : 2-6 : 7-*dibenzacridine* (VII).—Obtained from the foregoing tetrahydro-compound (0·4 g.) with selenium powder (0·3 g.) at 350° for 3 hours, this *compound* formed fine pale yellow needles, m. p. 110°, from ethanol and gave with sulphuric acid a yellow colour (Found : C, 89·2; H, 5·5. $C_{23}H_{17}N$ requires C, 89·8; H, 5·5%). The picrate formed light orange needles (from nitrobenzene), m. p. 256° (decomp. at >232°).

1-*Ethyl*-1' : 2' : 3' : 4'-*tetrahydro*-3 : 4-6 : 7-*dibenzacridine*.—Obtained from β-naphthol (3 g.), the ethyl-amine (3 g.), and paraformaldehyde (0·6 g.), this *isomer* formed fine yellowish needles (from ethanol), m. p. 140°, giving with sulphuric acid an orange-yellow colour (Found : C, 88·9; H, 6·5%). The picrate formed from nitrobenzene orange leaflets, m. p. 289°.

3''-tert.-*Butyl*-1' : 2 : 3' : 4'-*tetrahydro*-3 : 4-6 : 7-*dibenzacridine*.—Prepared from 6-*tert.*-butyl-2-naphthol (2 g.), the ethyl-amine (2 g.), and paraformaldehyde (0·5 g.), by way of a picrate, orange-yellow leaflets (from ethanol), m. p. 257—258° (decomp. at >232°), the *butyl* derivative crystallised from ethanol in fine yellowish needles, m. p. 154° (Found : C, 88·0; H, 7·7. $C_{27}H_{29}N$ requires C, 88·3; H, 7·9%).

1-*Ethyl*-3 : 4-6 : 7-*dibenzacridine* (VIII).—The corresponding tetrahydro-compound (0·5 g.) and selenium powder (0·3 g.) gave this *compound* as fine pale yellow needles (0·3 g.) (from ethanol), m. p. 158° (Found : C, 89·3; H, 5·4%). The picrate formed yellow leaflets, m. p. 276°, from ethanol.

2 : 5-*Dimethyl*-1-(5 : 6 : 7 : 8-*tetrahydro*-2-*naphthyl*)*pyrrole*.—5 : 6 : 7 : 8-Tetrahydro-2-naphthylamine (5 g.), acetonylacetone (5 g.), and acetic acid (3 drops) were heated for 16 hours at 170—180°, and the reaction product fractionated in a vacuum. The *pyrrole* (5 g.) was a pale yellow oil, b. p. 200—202°/16 mm., $n_D^{21·5}$ 1·5790, giving a positive reaction in the pinewood test (Found : C, 85·2; H, 8·5. $C_{16}H_{19}N$ requires C, 85·3; H, 8·4%).

2 : 5-*Dimethyl*-1-(3-*ethyl*-5 : 6 : 7 : 8-*tetrahydro*-2-*naphthyl*)*pyrrole* (5 g.) formed a viscous pale yellow oil, b. p. 215—216°/17 mm. (Found : C, 85·2; H, 9·0. $C_{18}H_{23}N$ requires C, 85·4; H, 9·1%).

8-*Ethyl*-1' : 2' : 3' : 4'-*tetrahydro*-2 : 4-*dimethyl*-5 : 6-*benzoquinoline* (IX).—3-Ethyl-5 : 6 : 7 : 8-tetrahydro-2-naphthylamine (2 g.) and acetylacetone (2 g.) were refluxed for 2 hours; sulphuric acid (12 c.c.)

was added to the cold mixture, and the whole heated on a water-bath for 1 hour, poured on ice, and basified with aqueous ammonia. The reaction product was taken up in ether and yielded, on vacuum-fractionation in a vacuum, an oil (1·8 g.), b. p. 210—212°/16 mm., which solidified, then formed from light petroleum (b. p. 60—80°) prisms, m. p. 50° (Found: C, 85·0; H, 9·0. $C_{17}H_{21}N$ requires C, 85·3; H, 8·8%). Its picrate formed shiny yellow needles, m. p. 97°, from ethanol.

This reaction similarly yielded 1′ : 2′ : 3′ : 4′-*tetrahydro*-5 : 6-*benzoquinoline* as a pale yellow oil, b. p. 214—216°/17 mm., $n_D^{21\cdot5}$ 1·6125 (Found: N, 6·5. $C_{13}H_{17}N$ requires N, 6·6%). This material did not solidify on prolonged storage in the refrigerator, but a yellow picrate, m. p. 223—224°, could be prepared.

1″ : 2″ : 3″ : 4″-*Tetrahydro*-5 : 6-*benzindeno*(3′ : 2′-2 : 3)*indole* (X).—5 : 6 : 7 : 8-Tetrahydro-2-naphthylhydrazine hydrochloride was prepared by reduction of the appropriate diazo-compound (from the base, 5 g.) with stannous chloride (25 g.) in hydrochloric acid. A solution of this (1 g.), indan-1-one (1 g.), and sodium acetate (1 g.) in ethanol (20 c.c.) was refluxed for 1 hour, and the crude hydrazone precipitated on dilution with water was heated for a few seconds with a solution of hydrogen chloride in acetic acid. The *indole* obtained on dilution with water formed colourless needles (1 g.), m. p. 297°, from ethanol (Found: C, 87·9; H, 6·4. $C_{19}H_{17}N$ requires C, 88·0; H, 6·5%).

3 : 4 : 1″ : 2″ : 3″ : 4″-*Hexahydro*-1 : 2-6 : 7-*dibenzocarbazole* (XI).—Prepared as above from the hydrazine hydrochloride (1 g.) and 1-tetralone (1 g.), this *compound* formed fine colourless prisms (1·2 g.) (from ethanol), m. p. 190° (Found: C, 87·6; H, 6·6. $C_{22}H_{19}N$ requires C, 87·9; H, 6·9%). The picrate formed brown-violet leaflets, m. p. 175°, from ethanol.

3 : 4 : 5′ : 6′ : 7′ : 8′ : 1″ : 2″ : 3″ : 4″-*Decahydro*-6 : 7-*benzonaphtho*(2′ : 3′-1 : 2)*carbazole* (XII).—Prepared from 1-keto-1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydroanthracene (1 g.) and the hydrazine hydrochloride (1 g.), this hexacyclic compound formed fine colourless prisms (1·5 g.) (from ligroin), m. p. 208° (Found: C, 87·9; H, 7·3. $C_{24}H_{23}N$ requires C, 88·0; H, 7·6%). The picrate formed deep violet needles, m. p. 203°, from ethanol.

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659. *The Influence of Configuration on the Thermal Stability of N-Menthylphthalamic Acids.*

By A. KILLEN MACBETH, J. A. MILLS, and W. G. P. ROBERTSON.

The results obtained on heating the epimeric menthylamines with phthalic acid or anhydride confirm current views on their configurations. Phthalamic acids derived from *neo*- and *neoiso*-menthylamines resist cyclisation to phthalimides, indicating that these bases have the *cis*-configuration of amino- and *iso*propyl groups.

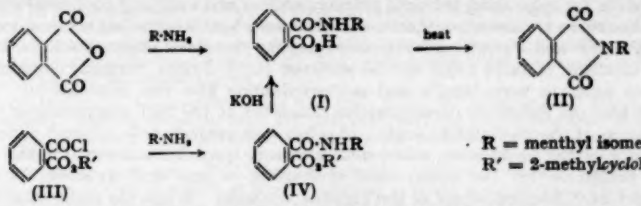
Mixtures of menthylamines may be separated by means of the reaction with phthalic anhydride, and isolation of (±)-*neoiso*menthylamine has been achieved in this way.

Difficulties were encountered when using competitive esterification to determine the relative reactivities of epimeric menthols.

FOLLOWING the successful use of *N*-(−)-menthylphthalamic acid as a resolving agent for alcohols (Human and Mills, *J.*, 1949, S 77; Macbeth, Mills, and Simmonds, *J.*, 1949, 1011), it was of interest to prepare the phthaloyl derivatives of other epimeric menthylamines as potentially useful resolving agents, and also for characterisation and purification of the bases. Hitherto, only (−)-menthylamine had been converted into the phthalamic acid and phthalimide (Clark and Read, *J.*, 1934, 1775). The investigation had to be suspended before the original aim was achieved, but the preliminary results are presented here because of their practical applications and their important bearing on the stereochemistry of menthylamines.

In agreement with Clark and Read we found that *N*-(−)-menthylphthalamic acid (I; R = menthyl) was very readily dehydrated to the imide (II; R = menthyl), boiling benzene being sufficient to effect the cyclisation. When (−)-menthylamine was heated with phthalic acid or anhydride in boiling toluene water was rapidly evolved, and the base was completely converted into the imide. Under the same conditions (+)-*neo*menthylamine readily afforded *N*-(+)-*neo*menthylphthalamic acid (I; R = *neo*menthyl), but all attempts to convert this acid into the imide (II; R = *neo*menthyl) have failed. Boiling it with chlorobenzene was without effect, and more severe treatment, such as refluxing it with nitrobenzene or with phosphoric oxide in chlorobenzene, caused extensive decomposition, with the production of several

unidentified compounds, none of which appeared to be *N*-(+)-*neo*menthylphthalimide. That the substance in hand actually was *N*-(+)-*neo*menthylphthalamic acid was confirmed by an alternative synthesis: the same acid was obtained by mild alkaline hydrolysis of the diastereo-



isomeric mixture of esters, (±)-*trans*-2-methyl*cyclo*hexyl *N*-(+)-*neo*menthylphthalamate (IV; R = *neo*menthyl), which had been prepared by converting (±)-*trans*-2-methyl*cyclo*hexyl hydrogen phthalate into the acid chloride (III) and treating this with (+)-*neo*menthylamine (Human and Mills, *loc. cit.*).

(−)-Menthylamine and (+)-*neo*menthylamine are epimeric, differing only in the configuration of the amino-group, and the above results indicate that *neo*menthylamine has the *cis*-configuration of the amino-group at $C_{(2)}$ with respect to the *iso*propyl-group at $C_{(4)}$. In *neo*menthylphthalamic acid the orientation of the substituents for any of the possible conformations of the strainless *cyclo*hexane ring provides enough steric hindrance to prevent ring-closure to an imide, whereas in the *trans*-epimer ring-closure is not hindered. However, examination of models of menthylphthalimide suggests that free rotation of the phthalimide group is strongly hindered, and therefore the formation of the *N*-(−)-menthylimide from an unsymmetrically substituted phthalic anhydride may lead to a diastereoisomeric mixture. This possibility is being tested.

The marked difference in reactivity between menthylamine and *neo*menthylamine was utilised in a convenient separation of the two bases. Hydrogenation of (−)-menthoxime in ammoniacal solution furnished a mixture of the two amines in which the *neo*-base predominated (77%), and treatment of the mixture with phthalic anhydride produced a mixture of phthalamic acids, of which only *N*-(−)-menthylphthalamic acid was cyclised in boiling toluene. The imide was separated from the unchanged *N*-(+)-*neo*menthylphthalamic acid, and from each of the products the amines were liberated by treatment with hydrazine. By applying this method of separation it could be shown that the standard preparation of (−)-menthylamine by the reduction of (−)-menthoxime with sodium in ethanol affords a product containing an appreciable amount of (+)-*neo*menthylamine (cf. Tutin and Kipping, *J.*, 1904, **85**, 65). The separation of the two bases does not require polarimetric control, and is equally suitable for active or racemic forms.

The other epimeric menthylamines, *iso*menthylamine and *neoiso*menthylamine, were expected to show the same difference in ease of cyclisation of derived phthalamic acids as was found for menthylamine and *neo*menthylamine. (±)-*iso*Menthoxime was hydrogenated in ammoniacal solution, and the resulting mixture of bases was converted by boiling with phthalic anhydride in toluene into a neutral product and an acid. The acid was evidently crude *N*-(±)-*neoiso*menthylphthalamic acid, as on treatment with hydrazine it afforded an inactive base different from known racemic menthylamines; this appears to be the hitherto unknown (±)-*neoiso*menthylamine, and the method of preparation indicates the expected *cis*-configuration at $C_{(2)}$–$C_{(4)}$. The separation was not as clear-cut in this case, and a study of active bases in the *iso*-series is desirable to clarify the position. There was some evidence of a slow cyclisation of the *neoiso*-phthalamic acid in boiling toluene. This could be the explanation for the much smaller proportion (52%) of crude *neoiso*-phthalamic acid isolated compared with that of *neo*-acid (77%) in the previous experiment (it is assumed that about the same proportion of *cis*-amine will be produced in hydrogenations of menthoxime and *iso*menthoxime), and why the fraction containing (±)-*iso*menthylphthalimide was a mixture from which a pure compound could not be isolated. Examination of models suggests that the steric hindrance to ring-closure in *neoiso*menthylphthalamic acid may be much less than in the *neo*-acid. This point will be amplified in a later communication.

The usefulness of the phthaloyl derivatives is practically confined to the separation of mixtures. Although they crystallise readily, their complete purification by recrystallisation is apt to be tedious and wasteful, and better results follow if the crude phthaloyl derivatives are

decomposed and the amines purified through suitable salts, Schiff's bases, or formyl derivatives. The phthalimides and phthalamic acids are all cleaved by the action of hydrazine (Ing and Manske, *J.*, 1926, 2348), more readily if 2-ethoxyethanol is used as solvent.

This procedure for separating epimeric primary amines and assigning configurations to them should be applicable to amines other than menthylamines, but its scope has not yet been defined accurately. For *cis*- and *trans*-3-methyl*cyclo*hexylamine the steric effect should be small, and separation of mixtures of these could not be achieved (L. J. Frahn, personal communication). An attempt to separate bornylamine and *neo*bornylamine also was unsuccessful; the chief difficulty here was the extensive decomposition occurring at the high temperatures needed to effect ring-closure of the phthalamic acids. We have at present only utilised differences in thermal stability of the phthalamic acids, and, although quite satisfactory for the menthylamines, this procedure for the preferential cyclisation of one acid probably is the least controllable and least discriminatory of the possible methods. When the steric factors are less pronounced, and the expected difference in thermal stability of the derived phthalamic acids correspondingly less (*e.g.*, the carvomenthylamines), preferential cyclisation of one acid might be achieved in a lower-boiling solvent, such as benzene, but perhaps more readily by the addition of an insufficient amount of a specific dehydrating agent (*e.g.*, thionyl chloride, acetic anhydride, or trifluoroacetic anhydride).

Experimental.

N-(+)-neo*Menthylphthalamic Acid*.—(*a*) Phthalic acid (1·64 g.) and (+)-*neo*menthylamine (1·55 g.) were added to chlorobenzene (30 ml.), and the mixture was refluxed for 3 hours. The solid quickly dissolved and water was evolved. Next morning the crystals which had separated were collected (2·6 g.), and showed m. p. 225—227°. Recrystallisation from chlorobenzene afforded pure N-(+)-neo*menthylphthalamic acid* as large white needles, m. p. 226—227°, $[\alpha]_D^{18}$ +51° (*c*, 0·8 in acetone) (Found: C, 71·1; H, 8·2; N, 4·9. $C_{18}H_{23}O_3N$ requires C, 71·2; H, 8·2; N, 4·6%). The substance dissolved readily in dilute aqueous sodium hydroxide, from which it was precipitated unchanged by hydrochloric acid. It was moderately soluble in cold alcohol or cold acetone, but only sparingly in benzene, toluene, or chlorobenzene.

(*b*) (±)-*trans*-2-Methyl*cyclo*hexyl *N*-(+)-*neo*menthylphthalamate (Human and Mills, *loc. cit.*) was hydrolysed by refluxing it for an hour with a 10% solution of potassium hydroxide (6 mols.) in methanol. After steam-distillation, acidification of the aqueous alkaline solution precipitated a solid which had m. p. 227°, alone or when mixed with the material prepared as in (*a*) above.

Attempted Cyclisation of the Above Acid.—Prolonged refluxing of the acid with toluene or chlorobenzene did not cause separation of water, and on cooling of the solutions the unchanged acid separated almost quantitatively. Heating the acid a little above its m. p. in an open tube produced a sublimate of the unchanged acid, and a dark liquid which solidified on cooling, and after three crystallisations from light petroleum–ethanol afforded a white *substance* (2·4 g. from 5 g. acid), m. p. 138—139°, $[\alpha]_D^{27}$ +1·5° (*c*, 2 in chloroform). This was not *N*-(+)-*neo*menthylphthalimide (Found: C, 73·6; H, 8·1; N, 3·8. $C_{18}H_{23}O_2N$ requires C, 75·9; H, 8·1; N, 4·9%).

A solution of the acid (5 g.) in pure nitrobenzene (30 ml.) was refluxed for 45 minutes, then the solvent was removed *in vacuo*, and the resulting dark cheesy mass was recrystallised several times from aqueous methanol. White needles were obtained (0·5 g.) of a *substance*, m. p. 153·5—154° $[\alpha]_D^{27}$ +57·6° (*c*, 2 in chloroform) (Found: C, 66·1; H, 10·7; N, 6·0%). When refluxed with phosphoric oxide in chlorobenzene the acid yielded a yellow oil which did not crystallise.

None of the foregoing products could be reconverted into *N*-(+)-*neo*menthylphthalamic acid by boiling alcoholic alkali.

Separation of (−)-*Menthylamine and* (+)-neo*Menthylamine*.—(*a*) (−)-Menthone was converted into the oxime by the action of hydroxylamine acetate at room temperature (Read and Robertson, *J.*, 1926, 2209) and the crude oxime was distilled under reduced pressure. A solution of the freshly distilled oxime (47 g.) in methanol (50 ml.) was saturated with ammonia at 0°, then hydrogenated over Raney nickel during 1·5 hours at 50—70°/80 atm. The reaction mixture was filtered, boiled under reflux to expel ammonia, acidified (hydrochloric acid), and steam-distilled to remove methanol. The acid solution was then made alkaline (sodium hydroxide), and the liberated amines were steam-distilled into dilute hydrochloric acid. Evaporation of the acid under reduced pressure afforded a mixture of the menthylamine hydrochlorides in 90% yield.

The amines were liberated from an aqueous solution of these hydrochlorides by addition of alkali, and extracted into toluene (400 ml.). The toluene solution was dried (NaOH) and then mixed with a solution of phthalic anhydride (42 g.) in warm toluene (200 ml.). An exothermic reaction occurred, with separation of white solid, which dissolved when the mixture was boiled. The solution was refluxed with a water-separator attached until water was no longer evolved (1·5 hours). On the solution's being set aside overnight *N*-(+)-*neo*menthylphthalamic acid (50 g.) crystallised, and a further quantity (15·5 g.) was obtained by extraction of the mother-liquor with sodium carbonate solution; the total yield was 77·5%. Evaporation of the toluene yielded crude *N*-(−)-menthylphthalimide (16·5 g., 21%). Five recrystallisations from aqueous ethanol afforded the pure imide (6 g.), m. p. 107—108° (cf. Clark and Read, *loc. cit.*).

Four recrystallisations of the crude *N*-(+)-*neo*menthylphthalamic acid from large volumes of chlorobenzene caused considerable losses without much improvement in m. p. (218—220°). A portion of the impure acid (19 g.) was added to a solution of 12M-hydrazine hydrate (7·2 ml.) in 2-ethoxyethanol (70 ml.), and the mixture was refluxed for 4 hours. Addition of 5N-hydrochloric acid (150 ml.) and warming for 2 hours liberated the amine from the complex, then the solution was filtered, steam-distilled to remove 2-ethoxyethanol, and made alkaline, and the amine steam-distilled into dilute hydrochloric acid. Concentration of the solution yielded several crops of slightly impure (+)-*neo*menthylamine hydrochloride (total 9·7 g., 81%), $[\alpha]_D^{18}$ +18° (*c*, 2 in water), compared with $[\alpha]_D$ +21·5° recorded by Read and Robertson (*loc. cit.*).

(*b*) Several batches of (−)-menthylamine had been prepared by reducing (−)-menthoxime with sodium in ethanol (Wallach, *Annalen*, 1893, **276**, 296) and purifying the crude amine through its formyl derivative. The combined light petroleum mother-liquors from the recrystallisation of the formyl compound were evaporated and the residue was hydrolysed with boiling 15% hydrochloric acid, affording a mixture of menthylamines with α_D^{20} −15° (homogeneous). This mixture was treated with phthalic anhydride in boiling toluene, and 22% of it was recovered as crude *N*-(+)-*neo*menthylphthalamic acid, m. p. 212—217°, which afforded the pure acid after repeated recrystallisation from chlorobenzene.

(±)-neoiso*Menthylamine*.—(±)-Piperitone (50 g.), dissolved in alcohol (100 ml.), was hydrogenated at room temperature and 50 atmospheres' pressure over palladium–charcoal (3·5 g. of 10%), and the solution of crude (±)-*iso*menthone was converted into the oxime under the condition used for (−)-menthone. The resulting crude oily oxime solidified on chilling, and the combined material from three preparations was recrystallised from 60% ethanol until the m. p. was constant; the yield of (±)-*iso*menthoxime, m. p. 98—100°, was 25%.

The purified oxime was hydrogenated under the conditions used for (−)-menthoxime, but the mixture of menthylamines (92%) was isolated in the free state, and not as hydrochlorides. The mixture was refluxed for 1 hour with the calculated quantity of phthalic anhydride in toluene, with separation of water. On cooling, the solution deposited some solid, and the solid and the mother-liquor were worked up for acidic and neutral components by extraction with sodium carbonate solution. The yields of acidic and neutral products were 52% and 48% respectively (*i.e.*, quantitative recovery) on the assumption that they were menthylphthalamic acid and menthylphthalimide.

The phthalimide fraction was evidently a mixture, and after four recrystallisations from 75% ethanol, with considerable losses, the material still melted over the range 81—86°. It was not further examined at this stage.

The phthalamic acid as isolated had an indefinite m. p., 176—182° (decomp.) in a sealed tube, and this was not altered by recrystallisation from toluene, which was attended by large losses. It was concluded that the product was fairly pure *N*-(±)-neoiso*menthylphthalamic acid*, which was undergoing slow cyclisation during the heating with toluene (Found: C, 71·6; H, 8·2. $C_{18}H_{25}O_3N$ requires C, 71·2; H, 8·2%).

The crystalline acid and the material recovered from the mother-liquors of its crystallisation were combined and decomposed by hydrazine hydrate in boiling 2-ethoxyethanol, and the menthylamine was isolated as the hydrochloride. The salt (15·2 g.) was dissolved in warm water (60 ml.), and the solution was mixed with a solution of sodium picrate, made by dissolving sodium hydroxide (3·2 g.) and picric acid (18·2 g.) in the minimum quantity of hot water. A yellow solid separated at once, and after cooling overnight it was collected and washed with a little water; it had m. p. 165—172°; the yield was 30·7 g. Recrystallisation from ethanol containing a little water afforded pure (±)-neoiso*menthylamine picrate* (21·6 g.), m. p. 175·5—177° (sealed tube) (Found: C, 50·2; H, 6·4; N, 14·9. $C_{16}H_{24}O_7N_4$ requires C, 50·4; H, 6·4; N, 14·9%).

The picrate was dissolved in warm water, and the amine was liberated by the addition of sodium hydroxide solution, extracted with ether, dried (NaOH), and distilled through a short column of glass helices. The (±)-*neoiso*menthylamine had b. p. 101—102°/30 mm. and n_D^{27} 1·4622, and was obtained in a yield of 92% from the picrate, and of 20% from (±)-*iso*menthoxime. Standard methods afforded the *benzoyl*, m. p. 188° (Found: C, 78·5; H, 9·4; N, 5·4. $C_{17}H_{25}ON$ requires C, 78·8; H, 9·7; N, 5·4%), and the *phenylcarbamyl* derivative, m. p. 132—133° (Found: C, 74·5; H, 9·2; N, 10·8. $C_{17}H_{26}ON_2$ requires C, 74·5; H, 9·5; N, 10·9%).

Appendix: *The relative reactivities of epimeric menthols and menthylamines.*

In addition to the above new method for assigning configurations to cyclic primary amines, we briefly examined some of the published kinetic methods for determining configurations of menthols and menthylamines, and experienced difficulties in applying the competitive acylation technique of Read and Grubb (*J.*, 1934, 1779). These authors allowed menthols to react in pairs with an insufficient amount of an acid chloride in pyridine, and from the products calculated the relative reaction velocities of the menthols; with *p*-nitrobenzoyl chloride in pyridine at 25° these were 16·5, 12·3, 3·1, and 1·0 for menthol, *iso*menthol, *neoiso*menthol, and *neo*menthol, respectively.

The order of reactivities appears to be correct, but the numerical values are open to question. Experiments with menthol–*neo*menthol mixtures and *p*-nitrobenzoyl chloride carried out under Read and Grubb's conditions, but with various ratios of menthol to *neo*menthol instead of the fixed, exactly equal amounts used by Read and Grubb, showed that, when the composition of the menthol mixture was varied, the apparent ratio of reaction velocities, $R = k_{\text{menthol}}/k_{\text{neo}}$,

also varied over a considerable range (*ca.* 15—25). The calculations of R could only be approximate, as the yield of esters was less than the theoretical, *e.g.*, 88%, and some free *p*-nitrobenzoic acid was always present; with mixtures rich in *neo*menthol an insoluble by-product was often noted as well. The latter afforded some pyridine and *p*-nitrobenzoic acid when boiled with alkali, and may have been derived from an acylpyridinium complex, which probably is an intermediate in the esterification. To suppress the possible adverse influence of pyridine as solvent (cf. Mills, *J.*, 1951, 2332), some reactions were carried out in benzene with only a small excess of pyridine, but R still varied somewhat as the composition of the menthol mixture was varied.

We had already applied the procedure of Read and Grubb to a pair of relatively labile, but unhindered, epimeric alcohols, (−)-*trans*- and (+)-*cis*-4-*iso*propyl*cyclo*hex-2-en-1-ol (Gillespie, Macbeth, and Mills, *J.*, 1948, 996), and in this instance it gave satisfactory results: in pyridine at 25°, with *p*-nitrobenzoyl chloride sufficient to esterify one-half of the mixed alcohols, the observed ratio, k_{cis}/k_{trans}, was reasonably constant (range, 1·00—1·09) for mixtures containing from 30—60% of the *cis*-alcohol. Only traces of free *p*-nitrobenzoic acid were detected, and no insoluble pyridine complex.

It seems that the method of competitive esterification is less satisfactory for sterically hindered alcohols. One or more of the following factors may account for the inconsistent results with the menthol mixtures: (*a*) partial dehydration of the menthols; (*b*) a side-reaction, leading to the insoluble product and rapid enough to compete with the esterification; (*c*) a departure from the strictly bimolecular mechanism of reaction assumed in the calculation of R. Working with a constant ratio of menthol to *neo*menthol, as in Read and Grubb's experiments, can obscure the effect of these adverse factors, and lead to consistent, but not necessarily correct, values for R. There is no doubt that menthol is much more reactive than *neo*menthol (cf. Vavon and Couderc, *Compt. rend.*, 1924, **179**, 405; Zeitschel and Schmidt, *Ber.*, 1926, **59**, 2298), but the numerical value of the difference is in doubt, except in the few cases where rate constants have been determined separately for the epimers. The rather easy separation of *neoiso*- and *neo*-menthol achieved by Hückel and Niggemeyer (*Ber.*, 1939, **72**, 1354) suggests that the reactivities of this pair differ more widely than is indicated by Read and Grubb's figure.

The original results of competitive acylation studies on menthylamines were unsatisfactory, and at variance with other evidence (Read and Grubb, *loc. cit.*), and our experiments have not clarified the position. Read and Grubb found that *neo*menthylamine was rather more reactive than menthylamine when competing for aromatic acid chlorides in a two-phase system containing aqueous alkali, although the difference between the epimers was surprisingly small. We obtained a similar result from the homogeneous competitive reaction with benzoyl chloride in pyridine ($k_{neo}/k_{menthylamine} = 1{\cdot}44$), but when competing for phenyl *iso*cyanate in benzene (Davis and Ebersole, *J. Amer. Chem. Soc.*, 1934, **56**, 885) menthylamine reacted somewhat more readily than *neo*menthylamine (ratio, 1·32 : 1). A bimolecular mechanism was assumed for these reactions.

At present the method of competitive acylation should be discounted as a means of determining the configuration of these and similar amines. There is considerable evidence from the general properties of menthols and menthylamines (Read and Grubb, *loc. cit.*; Barton, *Experientia*, 1950, **6**, 316), and from non-competitive kinetic studies by Vavon and Chilouet (*Compt. rend.*, 1936, **203**, 1526), that menthylamine has the *trans*-configuration at $C_{(3)}$–$C_{(4)}$, and this is supported by the results in the first part of this paper, and the similar but less decisive observations by Read and Hendry (*Ber.*, 1938, **71**, 2544) on the course of thermal degradations of *N*-menthyl- and *N*-*neo*menthyl-glycine to *NN'*-dimenthyldiketopiperazines.

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JOHNSON CHEMICAL LABORATORIES,
UNIVERSITY OF ADELAIDE, AUSTRALIA.

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660. *Dithiols. Part XI.* The Reactions of Epoxides with Hydroxy- and Poly-thiols.*

By L. N. Owen and Peter N. Smith.

The reactions of propylene oxide and *cyclo*hexene oxide with 2-mercaptoethanol and with ethane-1 : 2-dithiol, in the presence of sodium ethoxide, have been studied. The oxides attack 2-mercaptoethanol preferentially at the thiol group, and they react with the dithiol to give mono- and di-addition products. 1 : 2-Di-(2-hydroxy*cyclo*hexylthio)ethane, the di-addition compound from *cyclo*hexene oxide and ethane-1 : 2-dithiol, has been obtained in two stereoisomeric forms, both of which differ from the substance described by Culvenor, Davies, and Heath (*J.*, 1949, 278). *trans*-2-Hydroxy*cyclo*hexyl 2 : 3-dimercaptopropyl sulphide (isolated as the triacetyl derivative) has been prepared from *cyclo*hexene oxide and propane-1 : 2 : 3-trithiol.

Compounds containing the ethylene oxide ring system reacts with thiols according to the general scheme :

$$-\overset{\diagdown O \diagup}{CH}-CH- + R\cdot SH \longrightarrow -CH(OH)\cdot CH(SR)-$$

For example, ethylene oxide with hydrogen sulphide gives 2-mercaptoethanol, whilst with ethanethiol it gives ethyl 2-hydroxyethyl sulphide; similarly, *cyclo*hexene oxide and propanethiol give 2-hydroxy*cyclo*hexyl propyl sulphide (Tschitchibabine and Bestougeff, *Compt. rend.*, 1935, **200**, 242; Nenitzescu and Scărlătescu, *Ber.*, 1935, **68**, 587; Woodward, *J.*, 1948, 1692). Thiolacetic acid (R = Ac) also reacts in the same way, to give the *S*-acetyl derivative of a hydroxy-thiol (Nylen and Olsen, *Svensk. Kem. Tidsk.*, 1941, **53**, 274; Sjoberg, *Ber.*, 1942, **75**, 13). If in the reaction of ethylene oxide with hydrogen sulphide the oxide is present in excess, the main product is di-2-hydroxyethyl sulphide (thiodiglycol); this clearly indicates that the primary product, 2-mercaptoethanol, reacts preferentially at its thiol rather than at its hydroxyl group with the second molecule of oxide. The present paper describes some exploratory experiments which have been carried out with the object of extending these reactions to the use of hydroxy- and poly-thiols.

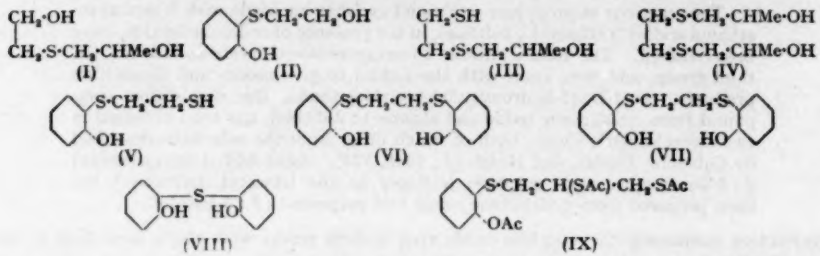
2-Mercaptoethanol reacted readily with 1 mol. of propylene oxide or *cyclo*hexene oxide in ethanol, in the presence of a catalytic amount of sodium ethoxide, to give 2-hydroxyethyl 2-hydroxypropyl sulphide (I) and *trans*-2-hydroxyethyl 2-hydroxy*cyclo*hexyl sulphide (II) respectively The structure allocated to (I) is based on analogy with the reaction of propylene oxide with alkoxides, in which the alkoxy-group becomes attached to the primary position (see, *inter al.*, Sadle, *J. Amer. Chem. Soc.*, 1950, **72**, 1251; cf. Todsen, Pollard, and Rietz, *ibid.*, p. 4000); the *trans*-structure is assigned to (II) on the assumption that the usual Walden inversion occurs when the oxide ring is opened. The preferential reaction of the oxides with the thiol group is therefore confirmed.

These results show that it would be impracticable to prepare *O*-derivatives of 2 : 3-dimercaptopropanol (" BAL ") by reaction of the latter with epoxides, unless the two thiol groups were previously protected (cf. Miles and Owen, *J.*, 1950, 2938). By the use of propane-1 : 2 : 3-trithiol, however, it should be possible, by reaction with 1 mol. of an epoxide, to obtain thio-analogues of such derivatives, *e.g.* :

$$R\cdot\overset{\diagdown O \diagup}{CH}-CH_2 + HS\cdot CH_2\cdot CH(SH)\cdot CH_2\cdot SH \longrightarrow R\cdot CH(OH)\cdot CH_2\cdot S\cdot CH(SH)\cdot CH_2\cdot SH$$

Preliminary experiments were carried out with ethane-1 : 2-dithiol in order to assess the extent to which the second thiol group becomes involved in the reaction. By using equimolecular proportions of dithiol and epoxide, a mixture of mono- and di-condensation products was formed, separable by fractional distillation. Thus, from propylene oxide, 2-hydroxypropyl 2-mercaptoethyl sulphide (III) and 1 : 2-di-(2-hydroxypropylthio)ethane (IV) were obtained, whilst *cyclo*hexene oxide gave *trans*-2-hydroxy*cyclo*hexyl 2-mercaptoethyl sulphide (V) and 1 : 2-di-(2-hydroxy*cyclo*hexylthio)ethane (the use of an excess of either oxide gave the bis-compounds exclusively). Shortly after the completion of this part of the work, Culvenor, Davies, and Heath (*J.*, 1949, 278) reported the formation of the last compound by a somewhat similar method, but gave m. p. 47—49°, whereas our product had m. p. *ca.* 74°. This difference could be attributed to stereoisomerism, since if a Walden inversion occurs at each opening of an oxide

ring the product formed when the second mol. of *cyclo*hexene oxide reacts with (V) can be either the *meso*- (VI) or the racemic-form (VII). On careful fractional recrystallisation, however, it was possible to isolate from the material of m. p. *ca.* 74° a small amount of an isomer, m. p. 100°; the residual portion, even after repeated recrystallisation from different solvents, had m. p. 72°, and no indication was obtained of the presence of any isomer of m. p. 47—49°.



The preparation was therefore repeated, this time under the exact conditions described by Culvenor, Davies, and Heath, but again no low-melting isomer could be obtained; fractional recrystallisation gave a very small amount of the high-melting compound, the main bulk having m. p. 72°. There can be little doubt that the isomer, m. p. 100°, is stereochemically pure (VI) or (VII); the material of m. p. 72° may be the other stereoisomer (in which case the compound of Culvenor *et al.* is possibly a metastable form) or it may be an inseparable mixture of the two. It is of interest that Mousseron, Bousquet, and Marret (*Bull. Soc. chim.*, 1948, 84) have obtained two stereoisomers of di-(2-hydroxy*cyclo*hexyl) sulphide (VIII). The bis-compound (IV) from the reaction with propylene oxide can also exist in *meso*- and racemic forms, but the product in this case was a low-melting solid and no indication was obtained of any separation of isomers.

Since the use of equimolecular quantities of epoxide and dithiol had given mixtures of mono- and di-addition products, an excess of propanetrithiol was used in its reaction with *cyclo*hexene oxide. The product, however, was again a mixture, and the boiling point was too high to allow of separation without serious decomposition, but this was possible after acetylation; fractional distillation then gave *trans*-2-acetoxy*cyclo*hexyl 2 : 3-bisacetylthiopropyl sulphide (IX).

The ethanedithiol required for these investigations was prepared in several different ways. Following Stocken's procedure (*J.*, 1947, 592) for the preparation of dithiols, it was obtained in 41% yield by reaction of a large excess of ammonium hydrogen sulphide with ethylene dibromide in methanol at room temperature. By reaction of ethylene dibromide with potassium thiolacetate, the crystalline diacetyl derivative of ethanedithiol was obtained (90%); this was also prepared (59%) from the ditoluene-*p*-sulphonate of ethylene glycol by the method of Chapman and Owen (*J.*, 1950, 579). Hydrolysis of the diacetyl derivative with methanolic barium methoxide gave the dithiol (*via* the barium salt) in 62% yield. The method recently described in *Organic Syntheses* (1950, **30**, 35) gives a 55—62% yield *via* ethylene di*iso*thiuronium bromide.

Experimental.

1 : 2-*Bisacetylthioethane*.—(i) Ethylene dibromide (30 g.) and potassium thiolacetate (40 g., 10% excess) in ethanol (200 c.c.) containing a few drops of thiolacetic acid were stirred and heated under reflux for 4 hours under nitrogen; potassium bromide separated from the red solution. After the mixture had cooled, ether was added until no more potassium salts were precipitated and the filtered solution was concentrated under reduced pressure. The residue was dissolved in ether, washed with water, dried (Na_2SO_4), and evaporated to a solid residue, which was recrystallised from light petroleum (b. p. 40—60°) giving 1 : 2-bisacetylthioethane (25·5 g., 90%), m. p. 69°. Mathias (*Chem. Abs.*, 1946, **40**, 2792) gives m. p. 68—69°.

(ii) 1 : 2-Ditoluene-*p*-sulphonyloxyethane (14 g.) in ethanol (150 c.c.) was treated with potassium thiolacetate (17·5 g., 100% excess) in ethanol (150 c.c.) at room temperature and then heated under reflux for 30 minutes. After cooling, the potassium toluene-*p*-sulphonate (13 g., 83%) which had been deposited, was filtered off and the filtrate was concentrated. The crude product was precipitated by addition of water, and recrystallised from light petroleum (b. p. 40—60°). The yield was 4 g. (59%), and the m. p. and mixed m. p. 69°.

Ethane-1 : 2-*dithiol*.—A stirred solution of the diacetyl derivative (40 g.) in dry methanol (100 c.c.), cooled to −10°, was slowly treated with 1·1N-methanolic barium methoxide (400 c.c.). The stirring was continued for 30 minutes at −10°, whereafter ice-cold dry ether was added until no more solid was

precipitated. The barium salts were rapidly filtered off under nitrogen and dissolved in 2N-aqueous hydrochloric acid; the dithiol liberated was isolated by extraction with ether. The crude material thus obtained was distilled to give ethane-1 : 2-dithiol (13·2 g., 62%), b. p. 51—52°/24 mm., n_D^{20} 1·5595.

Hydrolysis of the diacetyl derivative with methanolic hydrogen chloride or aqueous sodium hydroxide gave poor yields of the dithiol.

Reaction of Propylene Oxide with 2-Mercaptoethanol.—2-Mercaptoethanol (4 g.) and sodium (0·12 g.) were dissolved in dry ethanol (15 c.c.) contained in a pressure bottle. The solution was cooled to 0°, propylene oxide (3 g.) was rapidly added, and the vessel was sealed. Much heat was evolved, and when the initial reaction had subsided the bottle was heated at 100° for 2 hours. After being cooled, the solution was neutralised with carbon dioxide (a few drops of water being added), filtered, and concentrated. Distillation then gave *2-hydroxyethyl 2-hydroxypropyl sulphide* (4·05 g., 58%), b. p. 114—115°/2 mm., 102—103°/0·5 mm., n_D^{25} 1·5091 (Found: C, 44·7; H, 8·8; S, 23·4; thiol-S, 0. $C_5H_{12}O_2S$ requires C, 44·1; H, 8·9; S, 23·5%).

Reaction of cyclo*Hexene Oxide with 2-Mercaptoethanol.*—2-Mercaptoethanol (2 g.) in dry ethanol (5 c.c.) containing sodium (0·06 g.) was treated with *cyclo*hexene oxide (2·5 g.) and heated in a pressure bottle for 2 hours at 100°. The cooled solution was worked up as described above to give *2-hydroxyethyl 2-hydroxy*cyclo*hexyl sulphide*, (2·9 g., 63%), b. p. 122—123°/0·1 mm. The product solidified and on recrystallisation from light petroleum (b. p. 40—60°) had m. p. 46° (Found: C, 54·4; H, 9·2; S, 18·45; thiol-S, 0. $C_8H_{16}O_2S$ requires C, 54·5; H, 9·2; S, 18·2%).

Reaction of Propylene Oxide with Ethane-1 : 2-dithiol.—(i) Ethane-1 : 2-dithiol (5 g.), propylene oxide (3·0 g., 1 mol.), and sodium (0·12 g.) in ethanol (15 c.c.) were heated at 100° for 2 hours. Fractional distillation of the product gave *2-hydroxypropyl 2-mercaptoethyl sulphide* (1·75 g., 21%), b. p. 95°/0·7 mm. n_D^{19} 1·5570 (Found: thiol-S, 20·9. $C_5H_{12}OS_2$ requires thiol-S, 21·5%), and 1 : 2-*di*-(2-*hydroxypropyl-thio*)*ethane* (1·6 g., 20%), b. p. 140°/0·7 mm., n_D^{15} 1·5378 (Found: C, 45·9; H, 8·7; S, 30·3. $C_8H_{18}O_2S_2$ requires C, 45·7; H, 8·6; S, 30·5%), which solidified and had m. p. 38°; attempts to recrystallise the latter compound were unsuccessful.

(ii) Ethane-1 : 2-dithiol (5 g.), treated with propylene oxide (6 g., 2 mol.) under the above-mentioned conditions, gave only 1 : 2-di-(2-hydroxypropylthio)ethane (8 g., 73%).

Reaction of cyclo*Hexene Oxide with Ethane-1 : 2-dithiol.*—(i) Ethane-1 : 2-dithiol (5 g.) and *cyclo*hexene oxide (5 g.) in ethanol (15 c.c.), containing sodium (0·12 g.), were heated at 100° for 2 hours to give *2-hydroxy*cyclo*hexyl 2-mercaptoethyl sulphide* (2·08 g., 20%), b. p. 95—98°/0·1 mm., n_D^{20} 1·5587 (Found: C, 50·4; H, 8·7; S, 33·2; thiol-S, 16·8. $C_8H_{16}OS_2$ requires C, 50·0; H, 8·4; S, 33·3; thiol-S, 16·7%).

The residue, which solidified when cold, was distilled at 135° (air-bath)/2×10^{-4} mm., to give a product (1·52 g., 15%), m. p. 66—69°, which crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 68—69°. Further recrystallisation from the same solvent gave 1 : 2-di-(2-hydroxy*cyclo*hexylthio)ethane, m. p. *ca.* 74° (Found: C, 58·1; H, 9·3; S, 22·1. Calc. for $C_{16}H_{32}O_2S_4$: C, 57·9; H, 9·0; S, 22·1%). Three recrystallisations of this material from a mixture of benzene and light petroleum (b. p. 40—60°) gave an *isomer*, m. p. 100° (Found: C, 58·2; H, 9·2%). The material which remained in the mother-liquors was recovered (m. p. 70—72°), but further recrystallisation from the same solvent, from light petroleum, and from aqueous methanol failed to raise the m. p. above 72°. The m. p.s of the two forms were unchanged after each form had been heated above its m. p. for 10 minutes, and a mixture melted over the range 70—90°.

(ii) Ethane-1 : 2-dithiol (2·3 g.) in ethanol (30 c.c.) containing potassium hydroxide (2·8 g.) was treated with *cyclo*hexene oxide (4·9 g.) according to the method of Culvenor, Davies, and Heath (*loc. cit.*), to give 1 : 2-di-(2-hydroxy*cyclo*hexylthio)ethane (6·9 g., 95%), m. p. 69—72° (after distillation), raised after recrystallisation from light petroleum (b. p. 40—60°) to *ca.* 72°. The material was separated, as described above, into two forms, m. p. 97° (Found: C, 57·8; H, 8·7; S, 21·7%) and m. p. 72° (Found: C, 58·3; H, 9·1; S, 21·7%). There was insufficient of the higher-melting isomer for further recrystallisation. A mixture of the two isomers melted over the range 70—90° and mixed m. p.s with the corresponding compounds obtained as recorded in (i) showed no depression.

Reaction of cyclo*Hexene Oxide with Propane-1 : 2 : 3-trithiol.*—*cyclo*Hexene oxide (5 g.) was added to propane-1 : 2 : 3-trithiol (8 g.) (Miles and Owen, *J.*, 1950, 2943) in dry ethanol (150 c.c.) containing sodium (0·2 g.), and the homogeneous solution was set aside for 20 hours at ordinary temperature. The product was isolated as previously described; it was an almost colourless, viscous liquid (7·4 g.) (Found: thiol-S, 16·0. Calc. for $C_5H_{12}OS_3$: thiol-S, 27·0. Calc. for $C_{15}H_{28}O_4S_3$: thiol-S, 9·5%). Attempts to distil the material at 10^{-4} mm. were unsuccessful, and the crude mixture (7 g.) in dry pyridine (50 c.c.) was acetylated by treatment with acetic anhydride (10 g.). After 24 hours the solution was diluted with water and extracted with chloroform (100 c.c.). The chloroform solution was washed with dilute sulphuric acid, water, and saturated sodium hydrogen carbonate solution, dried ($MgSO_4$), and concentrated to a viscous liquid, which on distillation at 180—195° (air-bath)/5×10^{-4} mm. gave *2-acetoxy*cyclo*hexyl 2 : 3-bisacetylthiopropyl sulphide* (6·5 g.), n_D^{25} 1·5431 (Found: C, 50·3; H, 6·8; S, 25·2. $C_{15}H_{24}O_6S_3$ requires C, 49·5; H, 6·6; S, 26·4%). Light absorption: $\lambda_{max.}$ 2300 Å, ε 7500.

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
SOUTH KENSINGTON, LONDON, S.W.7.

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661. *Syntheses from Phthalimido-acids. Part III.* The Preparation of* DL- *and* L-*Asparagine from Phthalyl-*DL- *and* -L-*aspartic Anhydride.*

By F. E. KING and D. A. A. KIDD.

It has been shown that the action of ammonia on phthalyl-DL- and -L-aspartic anhydride leads to the formation of β-amides, since on removal of the phthalyl groups with hydrazine DL- and L-asparagine are obtained. In this the phthalylaspartic anhydrides resemble the corresponding phthalylglutamic anhydrides which with suitable reagents afford solely γ-derivatives, whereas, in general, anhydro-compounds of the other known acyl-aspartic and -glutamic acids give predominantly or exclusively α-substituted products.

DURING an investigation which led to the first recorded application of the phthalyl group as a protective device in peptide synthesis (King and Kidd, *Nature*, 1948, **162**, 776; *J.*, 1949, 3315), it was observed that the phthalyl-DL- and -L-glutamic anhydrides gave γ-substituted products on reaction with various amino-compounds, in contrast to the anhydrides of most acylamido-acids, from which α-derivatives or mixtures containing a preponderance of the α-isomer are generally formed. Treatment of the products with hydrazine removed the phthalyl group and thus opened a direct route to glutamine and other simple peptides of glutamic acid. The exclusive formation of γ-derivatives from the phthalylglutamic anhydrides extends also to their reactions with alcohols (King, Jackson, and Kidd, *J.*, 1951, 243), and the circumstances naturally suggested an extension of the enquiry into the chemically and biologically related aspartic acid series.

The anhydrides of acylaspartic acids in general give rise on ring-scission to α-substituted products, although certain inconsistencies have been reported in their reactions with both alcohols and amines. Benzoyl-L-aspartic anhydride, for example, gives with methanol a pure α-methyl ester (Pauly and Weir, *Ber.*, 1910, **43**, 661), whereas the action of benzyl alcohol on the toluene-*p*-sulphonylaspartic anhydride leads to a mixture of α- and β-benzyl esters in the ratio of approximately 4 : 1 (Bovarnick, *J. Biol. Chem.*, 1943, **148**, 151). The product obtained from the benzoyl-L-aspartic anhydride and ammonia has usually been regarded as the α-amide since it was apparently not identical with benzoylasparagine (Pauly and Weir, *loc. cit.*); its melting point corresponds approximately with that of benzoyl*iso*asparagine later recorded by Akizuki (*J. Biochem., Japan*, 1937, **25**, 43). Unpublished work by one of us with R. J. S. Beer (Thesis, Oxford, 1945) has confirmed the earlier inference by demonstrating the identity of the products obtained by the action of ammonia on the authentic methyl benzoyl-DL-aspartate and on the corresponding anhydride.

From carbobenzyloxy-L-aspartic anhydride α-amides normally appear to be formed, *e.g.*, from ammonia (Bergmann and Zervas, *Ber.*, 1932, **65**, 1192) and glycine ethyl ester (Bergmann, Zervas, and Fruton, *J. Biol. Chem.*, 1935, **111**, 235), but the product obtained with L-tyrosine ethyl ester, initially described as the α-amide (Bergmann and Zervas, *loc. cit.*), was subsequently shown to be the β-isomer (Bergmann, Zervas, Salzmann, and Schleich, *Z. physiol. Chem.*, 1934, **224**, 17). Acetylaspartic acid can be dehydrated with acetic anhydride either to an oxazolone (Bergmann, Stern, and Witte, *Annalen*, 1926, **449**, 277) or to a normal dicarboxylic anhydride (Harington and Overhoff, *Biochem. J.*, 1933, **27**, 338). Presumably products arising from the former will be α-derivatives but the constitution of compounds which may be derived from the true anhydride has not been ascertained.

Phthalylaspartic acid has been prepared by Piutti (*Gazzetta*, 1885, **14**, 473; 1886, **16**, 1) from L-aspartic acid and also from asparagine by heating them with phthalic anhydride at 150°. The configuration of the product was not indicated but from experience in the preparation of phthalylglutamic acid (King and Kidd, *loc. cit.*) it seemed probable that under these conditions racemisation would occur. This was verified by fusing a mixture of L-asparagine and phthalic anhydride: when the product, presumably an ammonium salt, was dissolved in water and acidified, a feebly active substance was precipitated which after recrystallisation had a melting point (225°) identical with that determined by Piutti.

On heating a mixture of DL-aspartic acid and phthalic anhydride first in boiling pyridine and then briefly in acetic anhydride, phthalyl-DL-aspartic anhydride was synthesised. With hot water the anhydride gave the DL-acid, m. p. 225°. When treated with ammonia under anhydrous conditions, the phthalyl-DL-anhydride was almost quantitatively converted into

* Part II, *J.*, 1951, 243.

a single amide which when submitted to hydrolysis with aqueous hydrazine at room temperature yielded the β-derivative, DL-asparagine, thus establishing the intermediate as phthalyl-DL-asparagine. The identification of the isomeric DL-aspartic monoamides is impracticable from melting-point determinations, and Bovarnick (*J. Biol. Chem.*, 1943, **148**, 151) has distinguished the racemic isomers by the difference in their rates of hydrolysis and in their crystalline form, the α-amide occurring in needles and the β-amide in prisms. The product from the hydrolysis of the phthalyl-amide crystallised in well-defined prisms and was further identified as β-DL-asparagine by the ninhydrin analysis of van Slyke *et al.* (*J. Biol. Chem.*, 1941, **141**, 671), the liberation of 0·9 mol. of carbon dioxide demonstrating the presence of the free α-carboxyl group.

The preparation of the optically active L-series started from the more readily accessible L-asparagine which though more stable than glutamine is readily converted by refluxing alcoholic hydrogen chloride (Fischer and Koenigs, *Ber.*, 1904, **37**, 4599) into diethyl L-aspartate. Treatment of a solution of this ester in ether with phthalic anhydride gave what is presumed to be the phthalamic acid which with thionyl chloride was cyclised to the liquid diethyl phthalyl-L-aspartate. Hydrolysis of the ester without affecting the phthalimido-group proved difficult but was finally achieved by a boiling mixture of acetic acid and concentrated hydrochloric acid. The crude phthalyl-L-aspartic acid was briefly heated with acetic anhydride from which on cooling the phthalyl-L-aspartic anhydride then crystallised. Phthalyl-L-aspartic acid was obtained from it by crystallisation from hot water.

By a procedure similar to that used in the DL-series, the L-anhydride was converted into phthalyl-L-asparagine, from which L-asparagine was obtained by hydrolysis with hydrazine. The specific rotation of the product determined in N/10-hydrochloric acid was found to be comparable with the published values for natural asparagine. Moreover the R_F values determined in different media were identical. The absence of appreciable amounts of the α-amide was also demonstrated in a two-dimensional chromatogram according to the method of Crumpler and Dent (*Nature*, 1949, **164**, 441), the first run being carried out along a copper carbonate band, which immobilises α-amino-acids by complex formation. No evidence of a β-amino-carboxyl grouping, such as is present in *iso*asparagine, was obtained on subsequent development and treatment with ninhydrin.

The phthalyl-L-aspartic anhydride was also treated with aniline, giving an apparently homogeneous anilide, which from the results of the ammonia reaction is assumed to be the β-anilide. Hydrolysis as before removed the phthalyl group giving L-aspartic acid β-anilide, the presence of the free α-carboxyl group being confirmed by the ninhydrin reaction.

Experimental.

Phthalyl-DL-aspartic Acid (cf. Piutti, *loc. cit.*).—An intimate mixture of phthalic anhydride (2 g.) and L-asparagine (2 g.), when heated in an oil-bath at 140—145°, first melted with effervescence and then partly resolidified. After 20 minutes' heating, the cooled product was dissolved in water, and crude phthalyl-DL-aspartic acid (2·4 g., 68%), m. p. 211—213° with softening from 203°, was precipitated by the addition of hydrochloric acid. Repeated crystallisation from water raised the m. p. to 220—223° alone or mixed with the product prepared *via* the anhydride (below).

Phthalyl-DL-aspartic Anhydride.—A suspension of phthalic anhydride (4·3 g., 1 mol.) and DL-aspartic acid (3·9 g., 1 mol.) in pyridine (75 c.c.) was boiled under reflux for 1½ hours. When the solvent had been removed under reduced pressure, the residue was boiled with acetic anhydride (50 c.c.) for 5 minutes. After concentration and cooling, *phthalyl-DL-aspartic anhydride* (4·7 g., 66%) separated in prisms, m. p. 220—221° (decomp.); it was also conveniently recrystallised from anhydrous dioxan (Found: C, 58·9; H, 2·7; N, 5·8. $C_{12}H_7O_4N$ requires C, 58·8; H, 2·9; N, 5·7%). On cooling of a solution of the anhydride in boiling water, *phthalyl-DL-aspartic acid* separated in rosettes of small needles, m. p. 225°; Piutti (*loc. cit.*) gives m. p. 225° but does not indicate the optical configuration of the product (Found: C, 54·9; H, 3·3; N, 5·2. $C_{12}H_9O_4N$ requires C, 54·8; H, 3·4; N, 5·3%). Crude phthalyl-DL-aspartic acid prepared by the fusion method is best purified by dissolution in hot acetic anhydride. The phthalylaspartic anhydride, m. p. 219—220°, then crystallises, and is converted by hot water into the acid, m. p. 225°, having zero rotation in aqueous sodium carbonate solution.

Phthalyl-DL-asparagine.—A supercooled solution of phthalyl-DL-aspartic anhydride (4 g.) in dioxan (75 c.c.) was treated with excess of anhydrous ethereal ammonia, and the bulky white ammonium salt collected, washed with ether, and rapidly dissolved in a little water. Acidification to Congo-red with 5N-hydrochloric acid precipitated *phthalyl-DL-asparagine* (3·9 g., 91%), m. p. 217° (decomp.), which crystallised from aqueous ethanol in minute prisms, m. p. 217—218° (decomp.) (Found: C, 55·0; H, 3·5; N, 10·1. $C_{12}H_{10}O_4N_2$ requires C, 55·0; H, 3·8; N, 10·7%).

DL-*Asparagine.*—A solution of the phthalyl-DL-asparagine (4 g.) in aqueous sodium carbonate (0·82 g. in 50 c.c.) was treated with hydrazine hydrate (1·7 g. of 50%) and set aside for 12 hours at room temperature. Acidification with dilute hydrochloric acid precipitated phthalylhydrazide which was removed by filtration, the filtrate then being rendered neutral to litmus with aqueous ammonia, and evaporated below 45° to 10 c.c. When the residue was treated with ethanol (10 c.c.) and set aside in the refrigerator, DL-asparagine slowly separated. It crystallised from aqueous ethanol in hydrated

rhombic prisms and decomposed at 280—290° after sintering from 210° (Found: Loss in wt. on drying at 110° in a high vacuum, 12·5. Calc. for $C_4H_8O_2N_2,H_2O$: H_2O, 12·0%. Found, in dried sample: C, 36·6; H, 6·0; N, 20·8. Calc. for $C_4H_8O_2N_2$: C, 36·4; H, 6·1; N, 21·2%). In a ninhydrin estimation (van Slyke *et al.*, *loc. cit.*), 5-c.c. portions of a 25-c.c. aqueous solution containing 205·6 mg. of synthetic DL-asparagine gave α-carboxy-amino-nitrogen, 3·40, 3·55 mg. (Calc.: 3·8 mg.).

Diethyl Phthalyl-L-aspartate.—Diethyl L-aspartate was obtained from the ester hydrochloride (Fischer and Koenigs, *loc. cit.*) by covering it with benzene and stirring it with diethylamine (1·2 mols.). Diethylamine hydrochloride was precipitated by dry ether, and the aspartic ester obtained by evaporating the filtrate (yield from L-aspartic acid, 76%).

A solution of diethyl L-aspartate (14·3 g.) in ether was treated with portions of powdered phthalic anhydride (11 g.) and set aside overnight. The mixture was then twice extracted with aqueous sodium hydrogen carbonate, the combined extracts were acidified, and the precipitated phthalamic acid was isolated with ethyl acetate. The crude compound, which did not crystallise, reacted vigorously at room temperature with thionyl chloride (35 c.c.). When the reaction was complete, excess of thionyl chloride was removed in a vacuum, and benzene distilled off from the residue, which was then taken up in ether and washed with water, aqueous sodium hydrogen carbonate, and water. Evaporation of the ether afforded *diethyl phthalyl-L-aspartate* (16·4 g., 78%), which was purified for analysis by distillation, the pure ester being collected as a colourless syrup, b. p. 180—190° (bath-temp.)/0·05 mm., n_D^{17} 1·5263 (Found: C, 60·3; H, 5·1; N, 4·4. $C_{16}H_{17}O_6N$ requires C, 60·2; H, 5·3; N, 4·4%).

Phthalyl-L-aspartic Anhydride.—Undistilled diethyl phthalyl-L-aspartate (16·4 g.) was heated under reflux in a mixture of acetic acid (145 c.c.) and concentrated hydrochloric acid (48 c.c.) for 1 hour. The solvents were then at once removed by evaporation at low pressure from a bath at 40—45°, and the residue was dried in a desiccator over sodium hydroxide. The product was swirled with acetic anhydride (35 c.c.) on the steam-bath and, as soon as a clear solution was obtained (2—3 minutes), it was rapidly cooled, thus causing *phthalyl-L-aspartic anhydride* to crystallise. When collected after a few hours at 2°, washed with ether, and dried over sodium hydroxide, the compound had m. p. 209—211°, unchanged by recrystallisation from ethyl acetate, from which it separated in needles (Found: C, 58·6; H, 3·2; N, 5·4. $C_{12}H_7O_5N$ requires C, 58·8; H, 2·9; N, 5·7%). The anhydride was dissolved in hot water; *phthalyl-L-aspartic acid* separated at 2° in tiny needles. After recrystallisation from water, the acid has m. p. 193°, $[\alpha]_D^{20}$ −59·5° (in ethanol) (Found: C, 55·0; H, 3·4; N, 5·2. $C_{12}H_9O_6N$ requires C, 54·8; H, 3·4; N, 5·3%).

Phthalyl-L-asparagine.—By a procedure similar to that described for the DL-isomer, phthalyl-L-aspartic anhydride was converted into phthalyl-L-asparagine. The L-amide (yield, 75%) crystallised from aqueous ethanol in rectangular prisms, m. p. 200—201° after sintering at 172—173° (Found: N, 10·8. $C_{12}H_{10}O_5N_2$ requires N, 10·7%).

L-Asparagine.—The phthalylasparagine (1 g.) was dissolved in aqueous hydrazine hydrate (2 c.c. of 20%) and set aside at room temperature for 48 hours, whereupon crystals of the phthalylhydrazide salt separated. The whole was then acidified with acetic acid, and the phthalylhydrazide removed by filtration. Acetone was added to the filtrate from which L-asparagine hydrate (0·2 g.) separated at 2°. Once recrystallised from aqueous acetone, it formed long needles, or rectangular prisms from water (Found, after drying at 110° under reduced pressure: C, 36·3; H, 5·9; N, 21·4. Calc. for $C_4H_8O_3N_2$: C, 36·4; H, 6·1; N, 21·2%); the monohydrate has $[\alpha]_D^{20}$ +32·6° in N/10-hydrochloric acid (1·1 mols.) (equiv. to +37·1° for the anhydrous compound). Recorded values show considerable variations with the concentration and quantity of mineral acid, but Champion and Pellet (*Compt. rend.*, 1876, **82**, 819) found $[\alpha]_D$ 37·27° in N/10-hydrochloric acid, and "Merck Index," 1940, p. 59, gives $[\alpha]_D^{20}$ +31° for the hydrate in N/10-hydrochloric acid.

The synthetic and natural asparagine (B.D.H.), when compared by partition chromatography, using *iso*amyl alcohol–pyridine (Edman, *Ark. Kemi, Min., Geol.*, 1945, *A*, **22**, No. 3) or phenol–ammonia and collidine (Dent, *Biochem. J.*, 1948, **43**, 169), showed identical R_F values, and were not separated by two-dimensional chromatography if the last two solvents (Dent, *loc. cit.*) were used.

Phthalyl-L-aspartic Acid β-Anilide.—Phthalyl-L-aspartic anhydride (0·5 g.) was shaken in ethereal suspension with aniline (0·3 c.c.), whereupon the solid material soon became pasty. The whole was extracted with aqueous sodium hydrogen carbonate, and the extract acidified with hydrochloric acid which precipitated the *β-anilide* (0·25 g.). Recrystallised from water, it separated as the *monohydrate* in microscopic rectangular prisms, m. p. 98—99° (Found: loss on drying in a vacuum at 65°, 5·0. $C_{16}H_{14}O_4N_2,H_2O$ requires H_2O, 5·1%. Found, in dried material: N, 8·4. $C_{16}H_{14}O_4N_2$ requires N, 8·3%).

L-Aspartic Acid β-Anilide.—The phthalyl-anilide (0·72 g.) was dissolved in aqueous hydrazine (2·2 c.c. of 10%) and after 48 hours the resulting partly crystallised mixture was acidified with acetic acid, stirred, and filtered from phthalylhydrazide. Addition of acetone to the filtrate precipitated a flocculent solid, which was separated centrifugally and washed with acetone. When its aqueous solution was diluted to turbidity with acetone and set aside at 2°, prisms of the *L-β-anilide*, m. p. 251—252° (decomp.), separated (Found: C, 57·2; H, 5·9; N, 13·4. $C_{16}H_{16}O_3N_2$ requires C, 57·6; H, 5·8; N, 13·5%). The anilide rapidly gave a deep colour with ninhydrin solution which imparted a mauve-purple stain to filter paper.

The authors thank the Medical Research Council for the award (to D. A. A. K.) of a research studentship, and Sir Charles Harington, F.R.S., and Dr. J. Walker for facilities enabling this work to be completed at the National Institute for Medical Research. They also gratefully acknowledge the assistance of Dr. P. N. Campbell, National Institute for Medical Research, in carrying out the chromatographic analyses.

THE UNIVERSITY, NOTTINGHAM. [*Received, July 20th*, 1951.]

662. *Totarol. Part II.**†

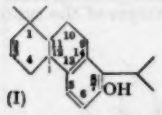
By W. F. Short and H. Wang.

(*With an Appendix on Absorption Spectra*, by J. D. S. Goulden.)

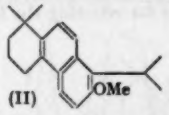
Further investigation of totarol, and particularly of the products of its partial dehydrogenation, indicate that this diterpene resinol is probably 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-7-hydroxy-1 : 1 : 12-trimethyl-8-*iso*propylphenanthrene (I). Its biogenesis is discussed in the light of its divergence from the " isoprene rule."

In Part I,* Short and Stromberg showed that totarol is a tricyclic resinol, $C_{20}H_{30}O$, and affords 7-hydroxy-1-methylphenanthrene and 1-methylphenanthrene on dehydrogenation. Catalytic reduction produced di- and tetra-hydro-compounds and, finally, a hydrocarbon, $C_{20}H_{34}$ (totarane), which was dehydrogenated to a hydrocarbon, $C_{18}H_{18}$, subsequently shown to be 1-methyl-8-*iso*propylphenanthrene (Short and Wang, *J.*, 1950, 991). Totarol afforded a hydrogen phthalate with phthalic anhydride at 140° but resisted dehydration and it was concluded that it contains a secondary alcoholic group. Subsequent oxidation experiments, under a variety of conditions, afforded a number of dimeric compounds but no ketone, and we have now found that totarol is a cryptophenol. The compound does not show a ferric chloride reaction in aqueous or alcoholic solution though it has a very slight but distinct solubility in 15% aqueous sodium hydroxide. The presence of a phenolic group is also indicated by the formation of substitution products, such as bromototarol, bromototaryl methyl ether, 2 : 4-dinitrophenylazototarol, m. p. 201—202°, and formyltotarol (2 : 4-dinitrophenylhydrazone, m. p. 230—231°), the last being obtained from totarol by the Gattermann hydrogen cyanide synthesis. Furthermore, aminototarol, m. p. 166—167°, obtained by the reduction of dinitrophenylazototarol with sodium dithionite, reacts with nitrous acid to give a diazonium salt which couples with β-naphthol in alkaline solution to give a red azo-dye. Spectroscopic data, reported in the Appendix by Dr. J. D. S. Goulden, are in full accord with the chemical evidence.

Ozonisation of totaryl acetate does not yield significant quantities of formaldehyde or acetone, indicating that the molecule does not contain either a terminal methylene group or an *iso*propylidene group, and this is consistent with the concentration of the three double bonds in an aromatic nucleus. The simplest interpretation of the degradation reactions is that totarol is 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-7-hydroxy-1 : 1 : 12-trimethyl-8-*iso*propylphenanthrene



(I)



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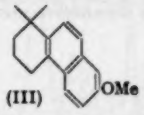

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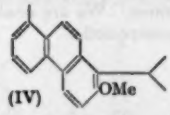


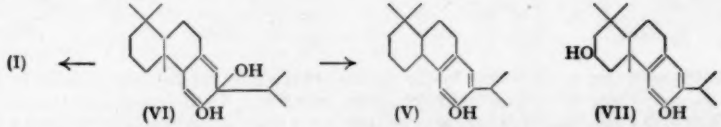
(IV)

(I), and this sturcture is supported by the results obtained by the dehydrogenation of methyl totaryl ether. Vigorous dehydrogenation with selenium affords 7-methoxy-1-methylphenanthrene in high yield, but under milder conditions three other compounds are obtained and may be separated by chromatography on alumina. The proportions in which these compounds (*A*, *B*, and *C*) are produced vary with the experimental conditions, the maximum yields being *A* 31%, *B* 29%, and *C* 17%. *A* (9·5%) and *B* (32%) are also produced by the dehydrogenation of methyl totaryl ether with sulphur. Compound *A* is converted into compound *C* by vigorous dehydrogenation with sulphur, and compound *B* is similarly converted into 7-methoxy-1-methylphenanthrene. Compound *A*, m. p. 109·5—110°, has the formula $C_{20}H_{24}O$, and affords a trinitrobenzene complex, m. p. 151·5—152°; its composition and relation to compound *C* suggest that it is 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1 : 1-dimethyl-8-*iso*propylphenanthrene (II). Compound *B*, $C_{17}H_{20}O$, m. p. 55·5—56°, is evidently produced by elimination of the *iso*propyl group from compound *A*; it affords a picrate, m. p. 105—106°, is demethylated by boiling pyridine hydrochloride to the corresponding phenol, m. p. 134—134·5°, and may be formulated as 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1 : 1-dimethylphenanthrene (III). Evidence for the

* Part I, *J.*, 1937, 516.

† This paper was presented in abstract at the International Congress of Pure and Applied Chemistry in New York, September, 1951.

attachment of the *iso*propyl group to $C_{(8)}$ in totarol (I) rests on the cryptophenolic properties of the resinol and on the assumption that no alkyl migration occurs during its simultaneous reduction and dehydration to totarane, which affords 1-methyl-8-*iso*propylphenanthrene on dehydrogenation. This is a reasonable assumption, but in view of the fact that the structure assigned to totarol cannot be built up from isoprene units, further experimental justification was desired, and was obtained by examination of compound *C* which still retains the *iso*propyl group. This compound, $C_{18}H_{28}O$, m. p. 144·5—145°, affords a picrate, m. p. 188—189°, and is demethylated by boiling pyridine hydrochloride to a phenol, m. p. 139—140°, which does not couple with 2 : 4-dinitrobenzenediazonium sulphate. We find that 7-hydroxy-1-methylphenanthrene couples readily with diazonium salts, and the failure of the diazo-coupling reaction with the phenanthrol derived from totarol is consistent with the attachment of the *iso*propyl group at position 8 (rather than 6) and therefore with structure (IV) for compound *C*. It was expected that distillation of the phenol with zinc dust would yield 1-methyl-8-*iso*propylphenanthrene but the product obtained was 1-methylphenanthrene, and removal of the hydroxyl group under less energetic conditions was therefore attempted. Unfortunately, the *iso*propyl group is simultaneously eliminated when the phenol is heated at *ca.* 290° with ammonium chloride, sodium acetate, and acetic acid, the resulting acetamido-compound being identical with 7-acetamido-1-methylphenanthrene, m. p. 241—242°, obtained by heating 7-hydroxy-1-methylphenanthrene with the same reagents. We therefore turned our attention to the synthesis of compound *C* by introducing an *iso*propyl group at position 8 in 7-hydroxy-1-methylphenanthrene, the structure of which was established by synthesis (Short, Stromberg, and Wiles, *J.*, 1936, 319). Application of the Gattermann hydrogen cyanide synthesis to 7-methoxy-1-methylphenanthrene affords a methoxy-aldehyde, m. p. 184·5—185·5° (semicarbazone, m. p. 332—334°), demethylated by boiling pyridine hydrochloride to a hydroxy-aldehyde, m. p. 206—207°, which does not couple with dinitrobenzenediazonium sulphate and is therefore regarded as 8-formyl-7-hydroxy-1-methylphenanthrene. This aldehyde is also obtained from 7-hydroxy-1-methylphenanthrene by the Gattermann synthesis, and methylation gives the methoxy-aldehyde, m. p. 184·5—185·5°, which is oxidised by potassium permanganate to 7-methoxy-1-methylphenanthrene-8-carboxylic acid. It was expected that methyl 7-methoxy-1-methylphenanthrene-8-carboxylate, and methylmagnesium iodide would yield 7-methoxy-1-methyl-8-*iso*propenylphenanthrene which could be reduced to compound *C*, but the product of the Grignard reaction is a hydrocarbon, $C_{19}H_{20}$, m. p. 168·5—170°, which may be 1 : 7-dimethyl-8-*iso*propylphenanthrene. Haller and Schaffer (*J. Amer. Chem. Soc.*, 1939, **61**, 2175), Fuson and his collaborators (*J. Org. Chem.*, 1948, **13**, 496 and earlier papers), and Richtzenhain and Nippus (*Ber.*, 1949, **82**, 408 and earlier papers) have recorded the replacement of alkoxyl by alkyl groups by the action of Grignard reagents on sterically hindered aromatic cyanides and ketones. We are examining alternative methods for effecting the final stages of the synthesis of compound *C*.



Totarol thus belongs to the group of natural diterpenoids, represented by podocarpic acid, hinokiol, and ferruginol, containing an aromatic nucleus, and it is interesting that three of these compounds occur in the flora of New Zealand. Totarol and podocarpic acid differ from all the diterpenoids whose constitutions have so far been elucidated by breaking the "isoprene rule": the latter lacks the *iso*propyl group necessary to make up the final isoprene residue, and the aromatic nucleus of totarol is not divisible into isoprene units. It may well be that totarol is derived from a precursor which obeys the "isoprene rule," an *iso*propyl group subsequently migrating at the stage of the phytosynthetic process at which the aromatic system is produced. This step may resemble the santonin–desmotroposantonin rearrangement and the conversion of certain steroid dienones into aromatic compounds, both totarol (I) and ferruginol (V) being produced by dehydration of the hypothetical protototarol (VI). The natural occurrence of a dihydroxy-compound, hinokiol, probably (VII), may be significant in this connexion.

The reaction of the aromatic nucleus in totarol, podocarpic acid, and ferruginol with 3 mols. of benzoyl hydroperoxide is probably associated with the presence of the hydroxyl group. Fernholtz (*Ber.*, 1951, **84**, 110) has recently shown that some aryl methyl ethers are oxidised by

peracids to methyl 2-*o*-carboxyarylacrylates. Totarol consumes only 1·9 mols. of *o*-carboxybenzoyl hydroperoxide in ethereal solution, and totaryl acetate and bromototarol do not react with benzoyl hydroperoxide in chloroform solution.

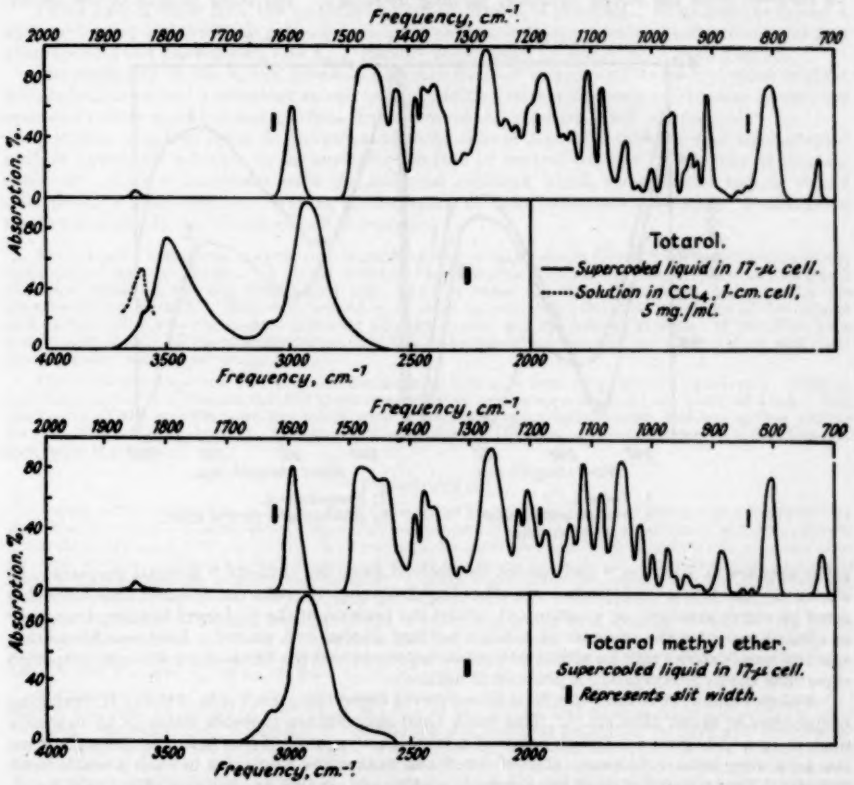
Synthetical work in relation to the suggested formula of totarol and its transformation products is in progress. The stereochemical problem is somewhat simpler than that involved in the synthesis of other diterpenoids, and the hydroaromatic rings probably have the *trans*-relationship.

Appendix.

By J. D. S. Goulden.

Infra-red Absorption Spectrum.—The infra-red spectrum of totarol shows a strong band due to a hydroxyl stretching frequency at 3500 cm.$^{-1}$ which is raised to 3600 cm.$^{-1}$ on dissolution of the substance in carbon tetrachloride. This small frequency shift with dilution shows that the hydroxyl group is not hydrogen bonded in the liquid state. Phenols which take part in inter-

Fig. 1.



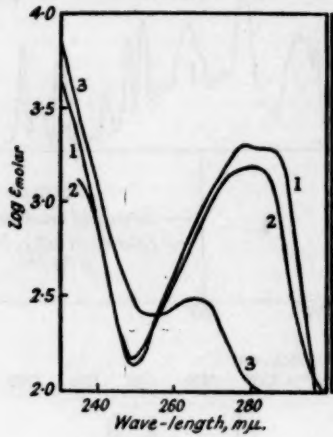
molecular hydrogen bonding are known to show a broad bonded-hydroxyl frequency at about 3300 cm.$^{-1}$ in the solid or liquid state. In dilute solution the intermolecular hydrogen bonds of such phenols are broken, so that the spectrum shows only the sharp frequency of the free hydroxyl group at about 3630 cm.$^{-1}$ Coggeshall (*J. Amer. Chem. Soc.*, 1947, **69**, 1620) has shown that the intermolecular hydrogen bonding of phenols can be prevented by steric factors. Chemical evidence shows the presence of an *iso*propyl group on the carbon atom *ortho* to the hydroxyl group. It is this *iso*propyl group which prevents the totarol molecules from aproaching each

other close enough to form a strong hydrogen bond in the liquid state. In dilute carbon tetrachloride solution, the hydroxyl frequency is still about 30 cm.$^{-1}$ lower than the value usually observed, suggesting that the neighbouring *iso*propyl group still slightly affects the vibrations of the hydrogen atom in the hydroxyl group. Intermolecular forces are no doubt responsible for a lowering of about 130 cm.$^{-1}$ in the value of the hydroxyl stretching frequency shown in the solid state. A small shoulder on the side of the 3500 cm.$^{-1}$ band occurs at 3560 cm.$^{-1}$, showing that some of the totarol molecules in the liquid state are not subject to these forces.

The absence of a strong absorption band in the 1650—1850-cm.$^{-1}$ region of the spectrum shows that the totarol molecule cannot contain a keto-group. The very weak band shown at 1850 cm.$^{-1}$ may be due to an aromatic nucleus in the totarol molecule. Since both totarol and its methyl ether show this band at the same intensity, the totarol band could not be attributed to a small amount of the phenol existing as the keto-tautomer. The strong frequency at 1594 cm.$^{-1}$ is low for a carbonyl group and is again shown by both substances at equal intensity.

The hydroxyl bonding frequency of totarol shows as a broad band at 1173 cm.$^{-1}$. A skeletal frequency occurs at 1175 cm.$^{-1}$, as shown by the spectrum of the methyl ether, and this cannot be resolved from the strong hydroxyl bending frequency. The ether linkage of the methyl

FIG. 2.



1, *Totarol.*
2, *Methyl totarol ether.*
3, *Totaryl acetate.*

FIG. 3.

1, *Bromototarol.*
2, *Bromototarol methyl ether.*

ether appears at 1052 cm.$^{-1}$ and cannot be resolved from the 1045-cm.$^{-1}$ skeletal frequency, as shown by the totarol spectrum. An ether-link frequency of 1052 cm.$^{-1}$ shows that the ether must be either aromatic or unsaturated, whilst the position of the hydroxyl bonding frequency of totarol indicates the presence of either a tertiary alcohol or a phenol. Evidence from other spectral bands shows that an aromatic nucleus is present and the ultra-violet absorption spectra show that the hydroxyl group is phenolic in nature.

A weak band at 3070 cm.$^{-1}$ can be resolved on the higher-frequency side of the C–H stretching frequencies at about 2900 cm.$^{-1}$. This weak band suggests the presence either of an aromatic nucleus or a C=C group. The presence of a large number of C–H bonds in the molecule gives rise to a very intense freqency at 2900 cm.$^{-1}$ and makes the resolution of such a weak band difficult. Two strong bands of the aromatic nucleus are evident at 1593 and about 1490 cm.$^{-1}$. It is difficult to resolve the latter band from the intense C–H bending frequencies at 1460 cm.$^{-1}$. Further frequencies of the aromatic nucleus occur below 1300 cm.$^{-1}$, together with the skeletal frequencies of the molecule. Slight differences between the spectra of the two molecules are to be expected in this region of the spectrum. No unconjugated C=C double bond frequency is observed at about 1650 cm.$^{-1}$.

The infra-red spectrum of totarol therefore confirms the presence of a phenolic group which is prevented from undergoing intermolecular hydrogen bonding by steric factors. No

unconjugated C=C double bonds are present in the molecule, but the presence of methylene and other groups containing C–H bonds is indicated. This structural evidence is in full accord with the formula obtained from the chemical evidence.

Ultra-violet Absorption Spectra.—The presence of an aromatic nucleus in a molecule usually gives rise to three close absorption maxima in the 250—275-mμ. region. These bands are not always resolved into the separate components, and the molar extinction values are generally about 200. A phenolic ring, however, gives rise to a more intense maximum at a higher wavelength. Such behaviour is shown by totarol and its acetate, as shown by the absorption curves of Fig. 2. This behaviour is parallel to that of phenol and its derivatives (cf. Table) (Morton, "The Application of Absorption Spectra to the Study of Vitamins, Hormones, and Co-enzymes," Hilger, 1942, p. 25).

	$\lambda_{max.}$ (mμ.)	log $\epsilon_{max.}$ (molar)		$\lambda_{max.}$ (mμ)	log $\epsilon_{max.}$ (molar)
Totarol	280—285	3·29	Phenol	273	3·38
„ methyl ether	281	3·185	Anisole	271	3·35
„ acetate	266	2·48	Phenyl acetate ...	261	2·36

These results show that the hydroxyl group of totarol is phenolic. If totarol contained a hydroxyl group attached to a non-aromatic ring containing double bonds, the above substitution effects would not have shown and $\epsilon_{max.}$ (molar) would most probably have been greater.

The similarity of the curves shown in Fig. 3 to those of totarol and its methyl ether confirm that bromination was a substitution reaction. Addition to double bonds would have caused the spectra to show more marked changes from those of the unbrominated compounds.

Addition of a few drops of concentrated hydrochloric acid or a few drops of concentrated sodium hydroxide solution to an alcoholic solution of totarol did not change the absorption spectrum. This is consistent with the chemical evidence which showed that totarol would only dissolve with difficulty even in concentrated sodium hydroxide solutions. A change in spectrum with pH was therefore not expected.

The infra-red absorption spectra were examined with a single-beam Grubb Parsons S3 spectrometer employing a rock-salt prisms. A Hilger–Schwarz thermocouple was used as a detector, with a chopped radiation beam. The cells were sealed with Araldite resin and their thicknesses measured by the interferometric method. They were heated in an oven to just above the melting points of the totarol and methyl ether and the compounds were allowed to run into the cells as liquids. If the filled cells were cooled slowly to room temperature, the liquids remained supercooled for several days and their spectra could easily be obtained.

The ultra-violet spectra were examined in 1-cm. quartz cells with ethyl alcohol as solvent. Totarol was examined with a Unicam S.P.500 spectrophotometer employing a constant slit width of 2 mμ. The remainder of the spectra were examined with a Beckman spectrophotometer and the author thanks Dr. W. F. Elvidge and Mr. L. Brealey of the Standards Division of Boots Pure Drug Co. Ltd. for supplying these data.

Experimental.

Totarol.—The resinol was extracted from the wood of *Podocarpus totara* and was purified as previously described (*loc. cit.*). A Zerewitinoff determination showed the presence of one atom of active hydrogen per molecule (Found, 0·98 atom) but there was no coloration with ferric chloride either in aqueous or in alcoholic solution. When a xylene solution of totarol was extracted with 15% aqueous sodium hydroxide and the filtered alkaline solution was acidified, a distinct flocculent precipitate was obtained, and the phenolic nature of the resinol was confirmed by coupling reactions with diazonium salts (below).

Totaryl Benzoate.—Benzoyl chloride (1 c.c., 1 mol.) was added to a solution of totarol (2·4 g.) in pyridine (10 c.c.) and, after the solution had been kept overnight, the product was precipitated with water, washed, and crystallised from alcohol, giving white plates (2·32 g., 71%) of *totaryl benzoate*, m. p. 144·5—145° (Found: C, 83·2; H, 8·5. $C_{27}H_{34}O_2$ requires C, 83·1; H, 8·7%).

Oxidation of Totarol and its Derivatives with Peracids.—Weighed quantities of each of the compounds were mixed with an excess of a standard solution of the peracid and kept at room temperature until oxidation was complete. A portion of the solution was removed from time to time and the peracid content determined with potassium iodide and sodium thiosulphate, a solution of the reagent being simultaneously assayed so that allowance could be made for spontaneous decomposition of the peracid. The previous results (*loc. cit.*) obtained with totarol and a 5% solution of benzoyl hydroperoxide in chloroform were confirmed, but different results were obtained with a 2% ethereal solution of *o*-carboxybenzoyl hydroperoxide.

	5% Benzoyl hydroperoxide in chloroform		2% *o*-Carboxybenzoyl hydroperoxide in ether	
	Atoms of oxygen absorbed	Hours	Atoms of oxygen absorbed	Hours
Totarol	3·2	48	1·9	96
Totaryl acetate	0	168	—	—
Bromototarol	0	192	0·2	96

Ozonisation of Totaryl Acetate.—(1) An ice-cold solution of totaryl acetate (0·2086 g.) in purified chloroform (10 c.c.) was ozonised for 7 hours in a stream of 5·8% ozone (about 9·4 l. per hour). The ozonisation vessel was followed by a wash-bottle containing water (10 c.c.) to collect volatile products, and the resulting solution and additional water (25 c.c.) were added to the residue obtained after removal of the chloroform from the ozonised solution at room temperature. The mixture was heated under reflux on the steam-bath for an hour and then distilled into ice-water (5 c.c.) until only 5 c.c. remained undistilled. M-Sodium acetate (25 c.c.), N-hydrochloric acid (25 c.c.), and saturated aqueous dimedone (50 c.c.) were added to the distillate, and the formaldehyde–dimedone compound (0·0033 g.), m. p. and mixed m. p. 184—186°, was collected after 12 hours. This yield is equivalent to 0·02 mol. of formaldehyde per mol. of totaryl acetate and, since Clemo and Macdonald (*J.*, 1935, 1295) have shown that compounds containing a doubly bound methylene group afford at least 0·2 mol. of formaldehyde under the conditions of the experiment, it is concluded that totaryl acetate does not contain this group.

(2) Totaryl acetate (0·02—0·06 g.) in purified acetic acid (12 c.c.) was ozonised for 4½ hours with 7·8% ozone (8·7 l. per hour), volatile products being collected in water (6 c.c.). The product was decomposed and the acetone, determined as described by Kuhn and Roth (*Ber.*, 1932, **65**, 1291), was equivalent to 0·30 and 0·28 *iso*propylidene group per molecule of totaryl acetate. Ozonisation of citral (0·05 g.) under the same conditions afforded acetone equivalent to 0·83 *iso*propylidene groups. Kuhn and Roth (*loc. cit.*) found that substances which contain an *iso*propylidene group afford 0·6—1·0 mol. of acetone, whereas several compounds not containing this group give 0—0·3 mol.

Bromototarol.—A solution of bromine (1 g.) in acetic acid (10 c.c.) was added in small portions with shaking to totarol (1 g.) in dry ether (10 c.c.). A positive starch–iodide test was obtained after the addition of 1·2 mols. of bromine, and the solvents were then removed below 50° and the soljd was recrystallised from methanol, giving prisms of *bromototarol* (1·02 g.), m. p. 89—89·5° (Found: C, 65·9; H, 7·9; Br, 22·0, 22·8. $C_{20}H_{29}OBr$ requires C, 65·75; H, 7·95; Br, 21·9%). The cryptophenol was not extracted from xylene solution by 15% aqueous sodium hydroxide. Bromototarol did not react with perbenzoic acid in 190 hours at room temperature but consumed 0·23 mol. of permonophthalic acid during 140 hours in ether–chloroform. Methyl totaryl ether (1 g.) in ether (10 c.c.) absorbed 1 mol. of bromine from 10% bromine–acetic acid and when the solid obtained by removing the solvents below 50° was crystallised from methanol containing a little chloroform successive crops of crystals, m. p. 128—129° (0·76 g.) and m. p. 121—124° (0·13 g.), were obtained. Repeated crystallisation from ethanol–chloroform gave long needles of *bromototaryl methyl ether*, m. p. 128·5—129° (Found: C, 66·45, 66·4; H, 8·4, 7·9; Br, 21·9. $C_{21}H_{31}OBr$ requires C, 66·5; H, 8·2; Br, 21·1%).

Aminototarol.—2 : 4-Dinitroaniline (25 g.) was dissolved in a hot mixture of acetic acid (150 c.c.) and concentrated sulphuric acid (15 c.c.), the solution was cooled rapidly, and amyl nitrite was added in small portions to the supension of finely divided sulphate until a clear solution was obtained. The diazonium sulphate was precipitated with ether (3 vols.) and purified by repeated precipitations with ether from acetic acid solution. A cold solution of the diazonium salt in acetic acid (150 c.c.) was slowly added to a solution of totarol (35 g.) in acetic acid (200 c.c.), and the red solid, collected after an hour, had m. p. 201—202° (decomp.) (12·7 g., 22%). Repeated crystallisation from alcohol did not alter the m. p. and 2 : 4-*dinitrophenylazototarol* was obtained in red plates which had m. p. 201—202° (decomp.) when rapidly heated or m. p. 196° (decomp.) when slowly heated (Found: C, 65·1; H, 6·8; N, 11·7. $C_{26}H_{32}O_5N_4$ requires C, 65·0; H, 6·7; N, 11·7%). Addition of water to the acetic acid mother-liquors precipitated a red solid, m. p. 61—71°, which became oily on attempted crystallisation and which was shown by chromatography to be a mixture of three or four compounds.

A solution of sodium dithionite (44 g.) in water (295 c.c.) was rapidly added to a boiling solution of 2 : 4-dinitrophenylazototarol (4·4 g.) in alcohol (365 c.c.), most of the alcohol was removed from the clear yellow solution by distillation, and the solid, precipitated from the residue by water, was repeatedly crystallised from alcohol, giving white plates, m. p. 160—162° (2·45 g., 89%). Recrystallisation from light petroleum afforded *aminototarol* in prisms, m. p. 166—167° with darkening at 160° (Found: N, 4·7. $C_{26}H_{31}ON$ requires N, 4·65%), which gave a hydrochloride, m. p. 204—208° (decomp.). Benzoyl chloride (1 c.c.) was added to a solution of the hydrochloride (1 g.) in pyridine (10 c.c.), and next morning water was added to precipitate an oil which rapidly solidified. Crystallisation from methanol gave white prisms of the *dibenzoyl* derivative, m. p. 142—143° (Found: C, 80·0; H, 7·8; N, 3·3, 3·3. $C_{33}H_{39}O_3N$ requires C, 80·2; H, 7·7; N, 2·75%). Aminototarol was readily diazotised in concentrated sulphuric acid–acetic acid, and the diazo-solution afforded a bright red precipitate with alkaline β-naphthol.

Formyltotarol.—Dry hydrogen chloride was passed for an hour into an ice-cold stirred mixture of totarol (5 g.), hydrogen cyanide (5·1 c.c., 7·5 mols.), powdered aluminium chloride (4·4 g., 1·9 mols.), and dry benzene (50 c.c.). The mixture was heated at 45° for 4 hours in a stream of hydrogen chloride, then poured on ice, and finally heated on the steam-bath for 3 hours. The benzene layer was separated, added to a benzene extract of the aqueous solution, washed, dried, and evaporated, giving a pale transparent glass. This was dissolved in light petroleum and adsorbed on Grade III alumina (160 g.). The single yellow band was eluted with light petroleum and afforded the hydroxy-aldehyde as a brownish glass (3·95 g., 72%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid in red prisms, m. p. 230—231° (decomp.) (Found: N, 11·4. $C_{27}H_{34}O_5N_4$ requires N, 11·3%).

Dehydrogenation of Methyl Totaryl Ether.—(A) *With selenium.* Four compounds, *A*, *B*, *C* (see below), and 7-methoxy-1-methylphenanthrene are produced by the dehydrogenation of methyl totaryl ether with selenium (2 parts). The composition of the product is determined by the duration and temperature of the dehydrogenation and to some extent by the scale of the operation, as illustrated by the examples recorded in the annexed Table.

The dehydrogenations were carried out by heating a mixture of methyl totaryl ether and powdered selenium (2 parts) in a flask deeply immersed in an electrically heated air-bath, the external temperature, indicated by a thermometer with its bulb level with the bottom of the flask, remaining constant to

within 5°. The product was extracted with hot acetone, the solution then being boiled with charcoal and evaporated to dryness. The residue was dissolved in benzene or light petroleum (b. p. 60—80°), and the constituents were separated by chromatography on a column of activated, " alkaline " alumina having an activity of II on the Brockmann scale (Brockmann and Schodder, *Ber.*, 1941, **74**, 73). A few typical experiments are described to illustrate the method of separation.

Expt. no.	Methyl totaryl ether, g.	Dehydrogenation, temp.	Dehydrogenation, time (hr.)	Recovered methyl ether, %	Dehydrogenation products (%) *A*	*B*	*C*	7-Methoxy-1-methylphenanthrene
(1)	4	300—305°	35	—	—	—	—	82
(2)	2	300—305	24	—	—	—	6	60
(3)	2	285—290	12	—	—	—	17	37
(4)	2	275—280	24	—	19	25	1	—
(5)	2	275—280	12	9	31	17	10	—
(6)	10	275—280	30	—	27	29	—	—
(7)	10	275—280	24	8	17	23	—	—
(8)	10	275—280	24	14	24	21	—	—
(9)	10	270—275	24	26	17	10	—	—
10)	10	275—280	12	84	9·5	2	—	—

(1) The residue (2·85 g.) from the acetone solution was dissolved in benzene (50 c.c.), adsorbed on a column of Grade II alumina (200 g.), and eluted with light petroleum (b. p. 60—80°) and benzene, the separation being followed by means of the fluorescent bands visible in ultra-violet light. A band with a violet fluorescence was eluted by light petroleum (600 c.c.), and the solution afforded an oily solid (0·29 g.). The next 150 c.c. of light petroleum removed an intermediate fraction giving a solid, m. p. 103—115° (0·12 g.). Elution with benzene (450 c.c.) removed a band with a blue fluorescence, and the solution afforded a solid, m. p. 121—125° (2·44 g., 82·5%), raised to 132—133° by crystallisation from alcohol. The m. p. was undepressed on admixture of this solid with 7-methoxy-1-methylphenanthrene (Short, Stromberg, and Wiles, *J.*, 1936, 321). The *picrate* was somewhat unstable but crystallised from alcoholic picric acid in orange needles, m. p. 140—141° (Found: C, 58·5; H, 3·7; N, 9·3. $C_{16}H_{14}O,C_6H_3O_7N_3$ requires C, 58·6; H, 3·8; N, 9·3%). The methyl ether did not yield a stable styphnate.

(2) The dehydrogenation product (1·27 g.) was dissolved in benzene and adsorbed on Grade II alumina (125 g.). On elution with light petroleum the first 450 c.c. of effluent contained only 0·02 g. of solid; the next 450 c.c. gave compound *C* (0·1 g.), isolated as picrate, m. p. 178—179° (see below). Subsequent elution with 75 c.c. of benzene gave a mixture (0·21 g.), and further elution with the same solvent (400 c.c.) afforded crude 7-methoxy-1-methylphenanthrene (0·89 g.), m. p. 124—128°, raised to 131—132° by one crystallisation from alcohol.

(5) The product was dissolved in light petroleum, adsorbed on Grade II alumina (125 g.), and eluted successively with light petroleum and benzene. The first portion of light petroleum (150 c.c.) produced a non-fluorescent solution containing a solid, m. p. 61—68° (0·18 g.), probably impure methyl totaryl ether. Light petroleum (145 c.c.) then removed a grey-black band and the solution afforded a solid, m. p. 91—98° (0·87 g., 46·5%), which gave compound *A*, m. p. 108—109·5° (0·58 g., 31%) after one crystallisation from alcohol. A dark violet fluorescent band was removed by light petroleum (230 c.c.), and evaporation of the solvent left an oily solid which afforded compound *B*, m. p. 53—55° (0·27 g., 17%), on crystallisation from alcohol. Benzene (300 c.c.) removed a band with a light violet fluorescence and evaporation of the solvent gave a solid (0·24 g., 13·5%) which gave compound *C*, m. p. 144—145° (0·18 g., 10%), on crystallisation from alcohol.

(7) The dehydrogenation products were adsorbed on a column of Grade II alumina (600 g.), black and dark violet bands being visible in ultra-violet light, and these were developed and eluted with light petroleum (b. p. 60—80°). The first effluent from the column was a non-fluorescent solution (400 c.c.) containing a mixture of solids (0·43 g.), and the lower part of the black band was removed from the column by the next 100 c.c. of solvent, the solution containing a solid (3·92 g.) which had m. p. 65—75° after crystallisation from ethanol. The rest of the black band, eluted with 240 c.c. of light petroleum, afforded a solid (3·55 g.; m. p. 103—108°) which gave compound *A*, m. p. 108—109° (1·62 g.), on crystallisation from ethanol. The dark violet band was removed in 650 c.c. of light petroleum, giving a solid (2·68 g.) which afforded compound *B*, m. p. 53—55° (1·63 g.), on crystallisation from methanol. The solid, m. p. 65—75°, obtained from the lower part of the black band and those recovered from the mother-liquors obtained in the crystallisation of compounds *A* and *B* were adsorbed on Grade I alumina (200 g.), and the column was percolated with light petroleum. The first effluent was a non-fluorescent solution (200 c.c.) containing a solid, m. p. 70—80° (1·08 g.), which afforded methyl totaryl ether, m. p. 92—93° (0·78 g.), on crystallisation from ethanol. A faint violet band was removed from the column by the next 250 c.c. of solvent and afforded a solid, m. p. 60—65° (2·07 g.), unaltered by one crystallisation from ethanol, which was evidently a mixture. The next 200 c.c. of effluent did not contain a solid, and a violet band, removed by 250 c.c. of solvent, afforded a solid m. p. 40—47° (0·56 g.), which gave compound *B*, m. p. 54·5—55·5° (0·18 g.), on crystallisation from methanol.

(B) *With sulphur.* Dehydrogenation of methyl totaryl ether with sulphur (4 atoms) at 220—260° afforded compound *C* as the main product, accompanied in some experiments by smaller quantities of compound *A*. In a typical experiment, methyl totaryl ether (5 g.) and sulphur (2·14 g.) were heated for 5 hours, the temperature being slowly raised from 220° to 260°. The mixture was then distilled, and the distillate dissolved in light petroleum and adsorbed on a column of Grade II alumina (300 g.). Elution with light petroleum (400 c.c.) removed a colourless band and afforded an oily solid (0·62 g.) which gave compound *A*, m. p. 105—106° (0·45 g., 9·5%), after two crystallisations from ethanol. A blue-violet band was removed by the next 150 c.c. of solvent, and the solution contained a solid, m. p.

87—115° (0·37 g.), which gave only a small quantity of solid, m. p. 130—134°, on crystallisation from ethanol. A violet band finally passed out of the column, and the solution (335 c.c.) contained a solid, m. p. 140—145° (1·14 g.), which afforded compound *C*, m. p. 147—148°, (0·91 g., 21%) on crystallisation from ethanol. Other dehydrogenations are summarised in the annexed Table.

Methyl totaryl ether, g.	Hours at 220—260°	Yields of dehydrogenation products (%) *A*	*C*	Methyl totaryl ether, g.	Hours at 220—260°	Yields of dehydrogenation products (%) *A*	*C*
5	5	9·5	21	20	8	—	23
10	8	4·0	28	20	8	—	25
10	10	—	32	15	8	—	31·5

1 : 2 : 3 : 4-*Tetrahydro*-7-*methoxy*-1 : 1-*dimethyl*-8-iso*propylphenanthrene* (*Compound* A).—This *compound* separated from methanol in rods, m. p. 109·5—110° (Found: C, 85·25; 85·0; H, 9·3, 9·4. $C_{20}H_{24}O$ requires C, 85·1; H, 9·2%). The picrate was unstable but the *trinitrobenzene complex* crystallised from alcohol in red needles, m. p. 151·5—152° (Found: N, 8·7. $C_{20}H_{24}O,C_6H_3O_7N_3$ requires N, 8·5%). Dehydrogenation with sulphur converted compound *A* into compound *C* (see below).

1 : 2 : 3 : 4-*Tetrahydro*-7-*methoxy*-1 : 1-*dimethylphenanthrene* (*Compound* B).—*Compound* B was purified by crystallisation from methanol and separated in matted needles, m. p. 55·5—56° (Found: C, 85·3; H, 8·3. $C_{17}H_{20}O$ requires C, 85·0; H, 8·3%). The *picrate* crystallised from alcohol in red needles, m. p. 105—106° when heated slowly or 94° when heated rapidly (Found: C, 59·2, 59·3; H, 5·05, 4·6; N, 9·0, 8·9. $C_{17}H_{20}O,C_6H_3O_7N_3$ requires C, 58·8; H, 4·9; N, 8·95%). The methyl ether and boiling hydrobromic–acetic acid afforded a black solid, m. p. 42—48°, but normal demethylation occurred when the ether (1·5 g.) and pyridine hydrochloride (4·5 g.) were stirred and boiled in an atmosphere of nitrogen for 2 hours. The resulting *phenol* (0·7 g., 50%) crystallised from benzene–light petroleum in small needles, m. p. 134—134·5° (Found: C, 85·0; H, 7·9. $C_{16}H_{18}O$ requires C, 85·0; H, 7·9%). The methyl ether (2 g.) was dehydrogenated by heating it with sulphur (0·56 g.) at 220—260° for 5 hours. The distillate (0·98 g.) afforded a solid, m. p. 123—125° (0·42 g., 23%), on crystallisation from alcohol, and further crystallisation raised the m. p. to 129—130°, undepressed on admixture with 7-methoxy-1-methylphenanthrene. The picrate melted at 141—142°, either alone or after admixture with authentic 7-methoxy-1-methylphenanthrene picrate.

7-*Methoxy*-1-*methyl*-8-iso*propylphenanthrene* (*Compound* C).—This compound was obtained by the dehydrogenation of methyl totaryl ether (above) or of compound *A*. A mixture of compound *A* (3·95 g.) and sulphur (0·9 g., 2 atoms) was heated to 220° and the temperature was slowly raised to 260° during 5 hours. The product was distilled at 2 mm. and the distillate (2·3 g.) was dissolved in light petroleum (b. p. 60—80°) and adsorbed on Grade II alumina (200 g.). The column was extracted with light petroleum (b. p. 60—80°), the effluent being collected in fractions. The first effluent (160 c.c.) was non-fluorescent and contained 0·17 g. of solid. Two subsequent fractions (125 and 250 c.c.) had a blue fluorescence and afforded solids, m. p. 98—125° (1·36 g.) and m. p. 125—134° (0·35 g.) respectively. Recrystallisation from ethanol gave white plates (1·21 g., 33%) of *compound* C, m. p. 144·5–145° (Found: C, 86·4, 86·7; H, 7·4, 7·9. $C_{19}H_{20}O$ requires C, 86·4; H, 7·6%). The *picrate* crystallised from alcohol containing picric acid in orange-red needles, m. p. 186—187° (Found: C, 60·9; H, 4·7; N, 8·7; $C_6H_3O_7N_3$, 45·9. $C_{19}H_{20}O,C_6H_3O_7N_3$ requires C, 60·9; H, 4·7; N, 8·5; $C_6H_3O_7N_3$, 46·5%). The *trinitrobenzene complex* consisted of orange needles, m. p. 208—209° (Found: C, 62·9; H, 4·8; N, 8·7. $C_{19}H_{20}O,C_6H_3O_6N_3$ requires C, 62·9; H, 4·8; N, 8·8%). Poor yields were obtained when the methyl ether was demethylated with boiling hydrobromic–acetic acid or with methylmagnesium iodide (1·4 mols.) in boiling tetrahydronaphthalene. The methyl ether (4·4 g.) and pyridine hydrochloride (12 g.) were boiled and stirred in an atmosphere of nitrogen for 2 hours and the product was repeatedly extracted with boiling dilute sodium hydroxide solution containing a little sodium sulphite. The solid, m. p. 131—134° (3·48 g., 84%), obtained by acidifying the filtered solution was crystallised from light petroleum (b. p. 60—80°) and gave prisms of the *phenol*, m. p. 139—140° (Found: C, 86·6; H, 6·9. $C_{18}H_{18}O$ requires C, 86·4; H, 7·2%). This phenol dissolved readily in hot 2N-sodium hydroxide; it did not couple with 2 : 4-dinitrobenzenediazonium sulphate in alkaline solution, whereas 7-hydroxy-1-methylphenanthrene gave a dark red precipitate of azo-dye under the same conditions. When a mixture of the phenol (0·5 g.) and zinc dust (10 g.) was heated and the vapour passed through a column of heated zinc dust (50 g.) a white sublimate (0·28 g.) was produced. This was purified by adsorption on a column of Grade II alumina (65 g.), elution with light petroleum (b. p. 60—80°) removing a blue violet fluorescent band and affording a white solid, m. p. 112—115° (0·19 g., 49%), which crystallised from alcohol in plates, m. p. 119·5—120° (Found: C, 93·05; H, 6·6. Calc. for $C_{18}H_{12}$: C, 93·75; H, 6·25%). This compound did not depress the m. p. of 1-methylphenanthrene and its identity was confirmed by a comparison of specimens of the picrates and styphnates. No further material was obtained by extracting the alumina column with other solvents.

7-*Hydroxy*-1-*methylphenanthrene*.—(1) Dehydrogenation of totarol (15 g.) with selenium (30 g.) as previously described (*loc. cit.*, p. 519) afforded 7-hydroxy-1-methylphenanthrene, m. p. 190—191° in 53% yield. (2) A 43% yield of the phenanthrol was obtained when 7-methoxy-1-methylphenanthrene (1 g.), 48% hydrobromic acid (100 c.c.), and acetic acid (100 c.c.) were boiled for 5 hours. (3) The methyl ether (2 g.) and pyridine hydrochloride (6 g.) were stirred vigorously at the b. p. for 2 hour in an atmosphere of nitrogen. The liquid was then cooled, the resulting solid was triturated with water, and the residue extracted with dilute aqueous sodium hydroxide (2 × 300 c.c.). Acidification of the filtered solution gave 7-hydroxy-1-methylphenanthrene, m. p. 190—191° (1·13 g., 60%).

This phenol coupled readily with benzenediazonium chloride and 2 : 4-dinitrobenzenediazonium sulphate.

7-Amino-1-methylphenanthrene.—(1) A mixture of 7-hydroxy-1-methylphenanthrene (2·08 g.), anhydrous sodium acetate (3·61 g.), ammonium chloride (2·57 g.), and acetic acid (4 c.c.) was heated at 285—295° for 16 hours. The product was extracted with hot dilute sodium hydroxide solution (2 × 400 c.c.) to remove a little unchanged phenol, and the residue was crystallised from alcohol, giving the crude amide, m. p. 233—235° (0·92 g., 37%). Further crystallisation from alcohol (charcoal) gave *7-acetamido-1-methylphenanthrene* as white prisms, m. p. 241—242° (Found: C, 82·1; H, 6·2; N, 5·7. $C_{17}H_{15}ON$ requires C, 81·9; H, 6·0; N, 5·6%). The corresponding amine was obtained in 70% yield by boiling the acetyl derivative (0·6 g.), hydrochloric acid (4 c.c.), water (2 c.c.), and alcohol (20 c.c.) for 5 hours. The hydrochloride was collected, warmed with dilute aqueous ammonia, and the *amine* crystallised from light petroleum (b. p. 60—80°) in clustered needles, m. p. 103—104° (Found: N, 6·4. $C_{15}H_{13}N$ requires N, 6·7%). (2) 7-Hydroxy-1-methyl-8-*iso*propylphenanthrene (2·5 g.; m. p. 139—140°), anhydrous sodium acetate (3·61 g.), ammonium chloride (2·57 g.), and acetic acid (4 c.c.) heated at 285—295° for 20 hours gave some unchanged phenanthrol (0·14 g., 6%), m. p. 134—137°, and 7-acetamido-1-methylphenanthrene (1·06 g., 43%), m. p. and mixed m. p. 241—242°. The phenanthrol (60%) was recovered when the mixture was heated at 225—235° for 18 hours.

8-Formyl-7-methoxy-1-methylphenanthrene.—(1) Hydrogen chloride was passed for an hour into a stirred, ice-cold mixture of 7-methoxy-1-methylphenanthrene (1·08 g.), hydrogen cyanide (1·4 c.c., 7·3 mols.), aluminium chloride (1·2 g., 1·8 mols.), and dry benzene (20 c.c.). After being heated at 45° for 2 hours, the mixture was diluted with ether, added to water, and distilled to remove ether, and the residue boiled for 3 hours. The product was collected in benzene, the solution being washed, dried, concentrated, and adsorbed on a column of Grade I alumina (100 g.). Elution with dry benzene afforded a single product, m. p. 183—184° (0·75 g., 61·5%), and crystallisation from alcohol gave *8-formyl-7-methoxy-1-methylphenanthrene* as pale yellow plates, m. p. 184·5—185·5° (Found: C, 81·6; H, 5·4. $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·6%). The *semicarbazone* had m. p. 332—334° (decomp.) (Found: N, 13·8. $C_{18}H_{17}O_2N_3$ requires N, 13·7%).

The methoxy-aldehyde (0·1 g.) was demethylated by boiling it for 20 minutes with pyridine hydrochloride (1 g.) in an atmosphere of nitrogen, and the resulting hydroxy-aldehyde crystallised from alcohol in yellow plates, m. p. 203—205°, which did not depress the m. p. of the aldehyde, m. p. 206—207°, prepared directly from 7-hydroxy-1-methylphenanthrene (see below).

(2) 7-Hydroxy-1-methylphenanthrene was converted into the hydroxy-aldehyde in 42—48% yield by using the method described above for the preparation of its methyl ether, except that the crude aldehyde was isolated directly from the benzene solution and purified by crystallisation from benzene and alcohol. *8-Formyl-7-hydroxy-1-methylphenanthrene* crystallised from alcohol in pale yellow plates, m. p. 206—207° (Found: C, 81·7; H, 4·8. $C_{16}H_{12}O_2$ requires C, 81·4; H, 5·1%). The 2 : 4-*dinitrophenylhydrazone* crystallised from nitrobenzene–light petroleum in brick red needles, m. p. 327° (decomp.) (Found: N, 13·6. $C_{22}H_{16}O_5N_4$ requires N, 13·5%). The aldehyde did not couple with 2 : 4-dinitrobenzenediazonium sulphate. The hydroxy-aldehyde (1 g.), methyl iodide (3 c.c.), potassium carbonate (0·6 g.), and acetone (30 c.c.) afforded the methyl ether, m. p. 184·5—185·5° (83%), when boiled for 12 hours.

7-Methoxy-1-methylphenanthrene-8-carboxylic Acid.—A solution of the corresponding aldehyde (0·5 g.) in acetone (40 c.c.) was stirred at 50° during the slow addition of an aqueous solution (30 c.c.) of potassium permanganate (1 g., equiv. to 4·75 atoms of oxygen). Heating was continued for 1½ hours, and the acid was isolated by saturating the mixture with sulphur dioxide at 0° and removing the acetone by distillation. The crude product (0·41 g., 77%) had m. p. 287—290° (decomp.), and *7-methoxy-1-methylphenanthrene-8-carboxylic acid* crystallised from acetone in white plates, m. p. 299—300° (decomp.) (Found: C, 76·8; H, 5·0. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·25%). The acid is sparingly soluble in hot aqueous sodium hydroxide. The acid (1·2 g.), powdered silver oxide (7·5 g.), methyl iodide (5 c.c.), and benzene (200 c.c.) were boiled for 15 hours and filtered hot to remove silver salts. The solid which separated from the filtrate had m. p. 189—191° (1·1 g., 87%); crystallisation from light petroleum gave colourless needles of *methyl 7-methoxy-1-methylphenanthrene-8-carboxylate*, m. p. 191—192° (Found: C, 77·2; H, 5·6. $C_{18}H_{16}O_3$ requires C, 77·2; H, 5·7%).

Methyl 7-methoxy-1-methylphenanthrene-8-carboxylate and Methylmagnesium Iodide.—A solution of the ester (1 g.) in dry benzene (40 c.c.) was slowly added at 0° to a stirred solution of methylmagnesium iodide (3 mols.), prepared from magnesium (0·26 g.), methyl iodide (0·9 c.c.), and ether (10 c.c.), and the mixture was boiled for 3 hours. The complex was decomposed with ice-cold dilute hydrochloric acid, and the product, isolated by extraction with benzene, was distilled at 2 mm. pressure from powdered potassium hydrogen sulphate (0·4 g.). The distillate, m. p. 146—155° (0·86 g.), was crystallised successively from alcohol and benzene–light petroleum, giving a *hydrocarbon* which separated in clusters of plates, m. p. 168·5—170° (Found: C, 91·6; H, 8·2. $C_{18}H_{18}$ requires C, 91·7; H, 8·1%). This compound gave a faint colour with tetranitromethane in chloroform and was recovered unchanged on attempted reduction under atmospheric conditions in alcoholic solution in presence of samples of palladium–strontium carbonate or platinum oxide catalysts capable of effecting rapid reduction of *iso*eugenyl benzoate to the dihydro-compound. The hydrocarbon afforded a *trinitrobenzene complex*, m. p. 177—179° (Found: N, 8·8. $C_{18}H_{18}.C_6H_3O_6N_3$ requires N, 9·1%), and its properties indicate that it is probably 1 : 7-dimethyl-8-*iso*propylphenanthrene.

We are grateful to Sir Robert Robinson, O.M., F.R.S., for his interest and for helpful discussion.

THE COLLEGE OF TECHNOLOGY, MANCHESTER.
RESEARCH LABORATORIES, MESSRS. BOOTS PURE DRUG CO. LTD.,
NOTTINGHAM.

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663. *Sesquiterpenoids. Part I. Evidence for a Nine-membered Ring in Caryophyllene.*

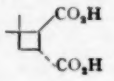
By D. H. R. Barton and A. S. Lindsey.

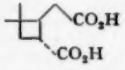
Evidence is presented that proves the second ring in caryophyllene to be nine-membered. Stepwise degradation limits the number of formulæ which are possible to three.

Caryophyllene, the principal sesquiterpene hydrocarbon of oil of cloves, has been the subject of numerous investigations since 1834, and a number of formulæ have been proposed (see Simonsen and Barton, " The Terpenes," Vol. III, Cambridge Univ. Press). For our knowledge of the chemistry of caryophyllene we are chiefly indebted to Simonsen and his colleagues in this country and to Ruzicka and his associates in Switzerland. It has been conclusively established that caryophyllene, $C_{15}H_{24}$, is bicyclic and contains two ethylenic linkages represented by the part expressions ·CMe:CH· (*a*) and >C:CH_2 (*b*).

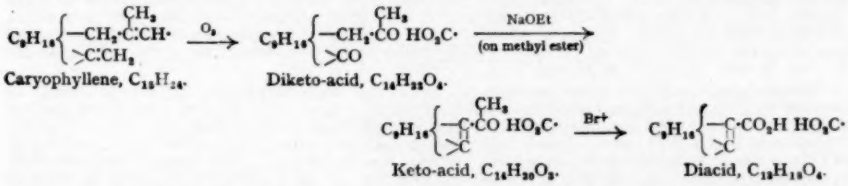
A fundamental advance in our knowledge of the chemistry of caryophyllene was the recognition that vigorous oxidative degradation afforded two *cyclo*butane acids, (+)-*trans*-norcaryophyllenic acid (I) (Evans, Ramage, and Simonsen, *J.*, 1934, 1806; Ramage and Simonsen, *J.*, 1935, 532; Ruzicka and Zimmermann, *Helv. Chim. Acta*, 1935, **18**, 219), the constitution of which was confirmed by Rydon's elegant synthesis (*J.*, 1936, 593; 1937, 1340), and (+)-*trans*-caryophyllenic acid (II) (Evans, Ramage, and Simonsen, *loc. cit.*; Barton, *J. Org. Chem.*, 1950, **15**, 457), the constitution of which has also been confirmed by synthesis (Campbell and Rydon, *Chem. and Ind.*, 1951, 312; cf. Dawson and Ramage, *J.*, 1950, 3523).

The ozonolysis of caryophyllene was first studied by Semmler and Mayer (*Ber.*, 1911, **44**, 3657). The two principal products were a $C_{11}H_{18}O_3$ keto-acid and a $C_{14}H_{22}O_4$ diketo-acid.


(I)


(II)

Both these acids contained one methyl ketone grouping as demonstrated by hypobromite oxidation. The reactions of the $C_{14}H_{22}O_4$ diketo-acid were investigated further by Ruzicka and Wind (*Helv. Chim. Acta*, 1931, **14**, 422) who showed that the methyl ester could be cyclised smoothly by sodium ethoxide to give an unsaturated keto-acid, $C_{14}H_{20}O_3$, which *still* contained the methyl ketone grouping, for hypobromite oxidation afforded a crystalline dicarboxylic acid, $C_{13}H_{18}O_4$, m. p. 148—149°. These changes must be interpreted in the following way:

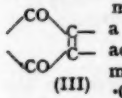


They are of importance because they show that the double bond (*a*) (see above) must be expanded to the part expression ·CH_2·CMe:CH·.

As Ramage and Simonsen (*J.*, 1935, 1581) first emphasised, much of the early work on caryophyllene is of doubtful value because only liquid products of unauthenticated homogeneity were obtained by starting with the liquid sesquiterpene itself. They therefore employed the crystalline " β-caryophyllene nitrosite " as starting material for conversion into other crystalline substances. Another crystalline derivative, eminently suited to stepwise degradation, was reported recently by Treibs (*Chem. Ber.*, 1947, **80**, 56), who showed that autoxidation of caryophyllene furnished in good yield a crystalline caryophyllene oxide, m. p. 64°. On further oxidation by potassium permanganate this gave a crystalline oxido-ketone, $C_{14}H_{22}O_2$, m. p. 61—62°. This reaction, confirmed by transformations summarised in the sequel, demonstrates that it is double bond (*a*), not (*b*), which is involved in oxide formation.

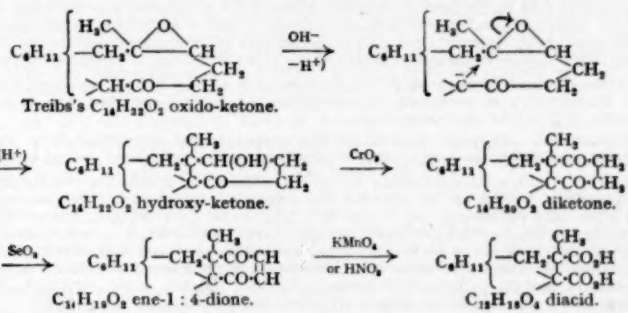
At the outset of our researches on caryophyllene there was no experimental evidence on the number of carbon atoms separating the two ethylenic linkages. We first attempted to settle this question in the following way. Treibs's oxido-ketone, $C_{14}H_{22}O_2$, treated with hydrogen chloride in chloroform solution, gave a crystalline chlorohydrin, m. p. 145—147°, which was smoothly oxidised by chromic acid to a chloro-diketone, $C_{14}H_{21}O_2Cl$, m. p. 90°. The latter was *not* an enolisable β-diketone, as some of the formulæ previously proposed for caryophyllene would require, since it showed only low-intensity ketonic absorption at 305—309 mμ. and gave a negative ferric chloride test.

The following experiments then furnished the required information. When Treibs's $C_{14}H_{22}O_2$ oxido-ketone was refluxed with methanolic potassium hydroxide it was smoothly, and almost quantitatively, isomerised to a highly crystalline substance, m. p. 148—149°. The ultra-violet and infra-red absorption spectra showed that this compound had one carbonyl and one hydroxyl group and, further, that it was saturated and, therefore, tricyclic; moreover, it gave no colour with tetranitromethane or with the Liebermann–Burchard reagent and afforded a 2 : 4-dinitrophenylhydrazone and a 3 : 5-dinitrobenzoate. On oxidation it gave in almost quantitative yield a saturated diketone, $C_{14}H_{20}O_2$, m. p. 51—52°, characterised as the mono-2 : 4-dinitrophenylhydrazone. Oxidation of this diketone with selenium dioxide furnished a pale yellow unsaturated diketone, $C_{14}H_{18}O_2$, m. p. 47—48°, in good yield. The absorption spectrum of this compound ($\lambda_{max.}$ 221, 367, and 369 mμ., ε = 14,700, 100, and 100, respectively) showed the presence of the chromophore $-CO-\overset{|}{C}=\overset{|}{C}-CO-$ in a *cisoid*-conformation (as in III). This conclusion was confirmed by oxidation with potassium permanganate in acetone solution, or with nitric acid, which afforded in good yield a saturated bicyclic dicarboxylic acid, $C_{12}H_{18}O_4$, m. p. 168—170° (decomp.). This acid readily furnished a crystalline anhydride, m. p. 42°, merely on being melted. The formation of the C_{12} acid proves the presence of the grouping $\cdot CO\cdot CH_2\cdot CH_2\cdot CH(OH)\cdot$ in the original tricyclic hydroxy-ketone, m. p. 148—149°.


(III)

A consideration of the mechanism of genesis of this hydroxy-ketone leads to a further important conclusion. In our opinion this compound must be formed by nucleophilic attack of the ketone carbanion upon the $-C(CH_3)-$ end of the oxide ring in Treibs's $C_{14}H_{22}O_2$ oxido-ketone. Thus the C_{12} bicyclic acid must be a *succinic* acid.

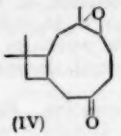
These conclusions can be summarised in the following partial formulæ:

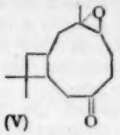


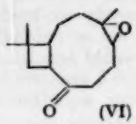
The residue, C_6H_{11}, must contain the dimethyl*cyclo*butane ring, or equivalent, and thus all the carbon atoms of caryophyllene are accounted for. It remains to discuss the fusion of the two halves of the molecule. There are three formulæ, (IV), (V), and (VI), which are formally possible as representations of Treibs's $C_{14}H_{22}O_2$ oxido-ketone. As yet, however, it is not possible to make a final decision, on the basis of our experiments, between these formulæ or between the corresponding formulæ (VII), (VIII), and (IX) for caryophyllene.

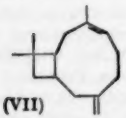
Whilst the experiments described above were in progress we received a reprint of a notable paper by Šorm, Dolejš, and Plíva (*Coll. Czech. Chem. Comm.*, 1950, **15**, 186) in which, mainly on the basis of the infra-red carbonyl frequency of Treibs's $C_{14}H_{22}O_2$ oxido-ketone, it was concluded that caryophyllene contained a nine-membered ring and was to be tentatively represented by either (VII) or (VIII). Our work is a chemical proof of the correctness of this view, and, with the reservation mentioned above, confirms the formulæ suggested for caryophyllene,

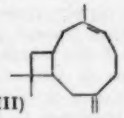
which would appear to be the first natural product proved to contain a nine-membered ring. The $C_{14}H_{22}O_3$ tricyclic hydroxy-ketone, (X), (XI), or (XII) on the basis of (VII), (VIII), or (IX), respectively, would also appear to be representative of a new type of tricyclic compound.

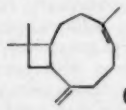

(IV)


(V)

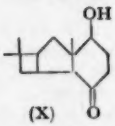

(VI)

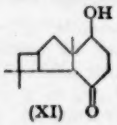

(VII)


(VIII)


(IX)

After our preliminary report (*Chem. and Ind.*, 1951, 313) there appeared a discussion of the constitution of caryophyllene by Dawson, Ramage, and Wilson (*ibid.*, p. 464), who would


(X)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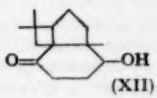
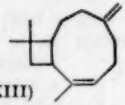

(XII)


(XIII)

appear to accept our proof of the nine-membered ring in caryophyllene, but propose for the hydrocarbon the formula (IX), which we omitted to mention in our preliminary paper, or (XIII). Of these (XIII) is, subject to the hitherto unquestioned validity of the evidence of Ruzicka and Wind (*loc. cit.*), inadmissible since it does not contain the grouping $\cdot CH_2 \cdot CMe{:}CH \cdot$.

Experimental.

M. p.s are uncorrected. All rotations were measured in chloroform solution; the values recorded have been approximated to the nearest degree. Ultra-violet absorption spectra were, unless specified to the contrary, determined in absolute ethanol solution by use of a Unicam Spectrophotometer, Model SP 500. Infra-red measurements were kindly carried out in chloroform solution by Mr. J. L. Hales on a modified Hilger double-beam spectrometer at the D.S.I.R. Chemical Research Station, Teddington.

Light petroleum refers throughout to the fraction of b. p. 40—60°. The caryophyllene used was obtained by fractionation of clove-bud sesquiterpenes. A typical specimen had b. p. 123—125°/10 mm., n_D^{20} 1·4988, $[\alpha]_D^{20}$ −9·15° (homogeneous).

Caryophyllene Oxide.—Caryophyllene oxide was prepared without difficulty by Treibs's method (*loc. cit.*). Best purified by low-temperature crystallisation from methanol, it had m. p. 61—62°.

Oxido-ketone, $C_{14}H_{22}O_3$.—Caryophyllene oxide was oxidised by potassium permanganate according to Treibs's directions. Working up afforded the $C_{14}H_{22}O_3$ oxido-ketone, best recrystallised at low temperature from light petroleum; m. p. 62—63°, $[\alpha]_D$ −134° (*c*, 4·81), $\lambda_{max.}$ 294—297 mμ. ($\varepsilon_{max.}$ 26). The oxido-ketone was also purified by chromatography over alumina which served to separate unchanged caryophyllene oxide (more easily eluted) from the oxido-ketone (more difficultly eluted). Treatment with semicarbazide acetate in the usual way furnished the semicarbazone which, recrystallised from chloroform–ethanol, had m. p. 235—236° (Found: C, 64·3; H, 8·7. Calc. for $C_{15}H_{25}O_2N_3$: C, 64·5; H, 9·0%). For this compound Šorm, Dolejš, and Plíva (*loc. cit.*) recorded m. p. 246·5°.

Chlorohydrin from $C_{14}H_{22}O_3$ *Oxido-ketone.*—The oxido-ketone (4·1 g.) in chloroform (50 ml.) was treated with a vigorous stream of hydrogen chloride at room temperature for 15 minutes. Removal of the chloroform *in vacuo* and recrystallisation from chloroform–light petroleum furnished the highly crystalline *chlorohydrin* (2·0 g.), m. p. 145—147° (decomp.) (Found: C, 64·9; H, 9·0. $C_{14}H_{23}O_3Cl$ requires C, 64·95: H, 9·0%), which gave a strongly positive Beilstein test.

Chloro-diketone, $C_{14}H_{21}O_3Cl$.—The chlorohydrin (2·0 g.) in "AnalaR" acetic acid (25 ml.) was treated with chromium trioxide (420 mg.) dissolved in water (1 ml.) and "AnalaR" acetic acid (9 ml.), and the homogeneous solution left for 16 hours at room temperature. Working up in the usual way and filtration through alumina in benzene solution furnished the *chloro-diketone* (650 mg.) which, recrystallised from chloroform–light petroleum, had m. p. 90°, $\lambda_{max.}$ 305—309 mμ. ($\varepsilon_{max.}$ = 70) (Found: C, 65·0; H, 8·3. $C_{14}H_{21}O_3Cl$ requires C, 65·45; H, 8·25%).

Reduction of $C_{14}H_{22}O_3$ *Oxido-ketone with Lithium Aluminium Hydride.*—The oxido-ketone (5 g.) in ether (100 ml.) was refluxed with an ethereal solution of lithium aluminium hydride (0·9 g.) for 1½ hours and then left overnight. After being worked up in the usual way, the resulting *oxido-alcohol* recrystallised from chloroform–light petroleum as white needles, m. p. 140—141°, $[\alpha]_D$ −118° (*c*, 4·40)

(Found : C, 75·3; H, 11·6. $C_{14}H_{24}O_3$ requires C, 75·0; H, 10·8%). That this compound was formed by reduction of the ketone grouping and that opening of the oxide ring had not occurred was proved by chromic acid oxidation which regenerated the original oxido-ketone.

Isomerisation of the $C_{14}H_{22}O_3$ *Oxido-ketone.*—The oxido-ketone (10 g.) was refluxed with 20% (wt./vol.) methanolic potassium hydroxide (150 ml.) for 6 hours. Dilution with water, extraction with ether, etc., and recrystallisation from chloroform–light petroleum gave the highly crystalline and sparingly soluble tricyclic *hydroxy-ketone* (9·0 g.), m. p. 148—149°, $[\alpha]_D$ −32° (*c*, 4·68), $\lambda_{max.}$ 288—292 mμ. ($\varepsilon_{max.}$ = 34) (Found : C, 76·0; H, 10·0. $C_{14}H_{22}O_3$ requires C, 76·0; H, 9·85%). This compound showed a maximum absorption in the infra-red at 2·8—2·9 μ., indicative of a hydroxyl group.

Treatment of the hydroxy-ketone with 3 : 5-dinitrobenzoyl chloride in pyridine solution on the steam-bath afforded the 3 : 5-*dinitrobenzoate* which, recrystallised from benzene–light petroleum, had m. p. 154—155° (Found : C, 61·1; H, 5·8. $C_{21}H_{24}O_7N_2$ requires C, 60·6; H, 5·8%). The 2 : 4-*dinitrophenylhydrazone*, recrystallised from methanol, had m. p. 150—151° (Found : N, 14·3. $C_{20}H_{28}O_6N_4$ requires N, 13·9%).

Tricyclic Diketone, $C_{14}H_{20}O_2$.—The tricyclic hydroxy-ketone (10 g.) in " AnalaR " acetic acid (80 ml.) was treated with chromium trioxide (5·4 g.) dissolved in water (4 ml.) and " AnalaR " acetic acid (6 ml.) and set aside at room temperature for 16 hours. Working up in the usual way afforded the crystalline tricyclic *diketone* (9·5 g.), which, recrystallised from cold light petroleum, had m. p. 51—52°, $[\alpha]_D$ −173° (*c*, 1·09), $\lambda_{max.}$ 292—294 mμ. ($\varepsilon_{max.}$ 70) (Found : C, 76·3; H, 9·15. $C_{14}H_{20}O_2$ requires C, 76·2; H, 8·9%). The *mono*-2 : 4-*dinitrophenylhydrazone* was prepared in the usual way. Purified by filtration in benzene solution through alumina and recrystallisation from aqueous methanol, it had m. p. 206—207° (Found : C, 60·6; H, 6·35; N, 14·4. $C_{20}H_{24}O_5N_4$ requires C, 60·0; H, 6·05; N, 14·0%). The diketone gave no response to tests for unsaturation. The ferric chloride test was also negative.

Tricyclic Diketone, $C_{14}H_{18}O_2$.—The tricyclic diketone mentioned immediately above (20 g.) in " AnalaR " acetic acid (200 ml.) was refluxed with powdered selenium dioxide (5 g.). There was a rapid deposition of selenium, and the solution became yellow. The refluxing was continued for 1 hour. The solution was cooled, filtered, diluted with water, and extracted with ether. Washing with dilute potassium hydroxide solution caused a further precipitation of selenium. The supernatant ethereal solution was decanted off. After evaporation of the solvent *in vacuo*, a benzene solution of the residue was filtered twice through alumina. In this way a good yield of the pale yellow, crystalline, tricyclic *diketone* was obtained. Recrystallised from cold light petroleum, it had m. p. 47—48°, $[\alpha]_D$ −297° (*c*, 1·32), $\lambda_{max.}$ 221, 367, and 369 mμ. ($\varepsilon_{max.}$ = 14,700, 100, and 100, respectively) (Found : C, 76·6; H, 8·15. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%). A somewhat less pure specimen of the diketone had $\lambda_{max.}$ 221 and 348 mμ. ($\varepsilon_{max.}$ = 11,500 and 120, respectively) (Found : C, 76·45, 76·4; H, 8·6, 8·1%). For further oxidation as described below the filtration through alumina was not necessary.

Dicyclic Dicarboxylic Acid, $C_{13}H_{18}O_4$.—The crude product from the selenium dioxide oxidation of the $C_{14}H_{20}O_2$ diketone (20 g.) (see above) was dissolved in " AnalaR " acetone (400 ml.) and oxidised by addition of potassium permanganate (70 g.) dissolved in the minimum of hot water on the steam-bath. The precipitated manganese dioxide was reduced by passing in an excess of sulphur dioxide, and the oily product extracted with ether. After removal of the ether, the crude acid, which was still oily, was dissolved in " AnalaR " acetone (100 ml.) and oxidised further by addition of potassium permanganate (10 g.) in the minimum of hot water. Working up of the product as before and crystallisation from hot water to which a little methanol had been added gave crude *dicarboxylic acid* (13 g.). After further recrystallisation from the same solvent it was obtained as fine leaflets, m. p. 168—170° (decomp.), $[\alpha]_D$ −4° (*c*, 1·20) (Found : C, 63·6; H, 8·15%; equiv., 113. $C_{13}H_{18}O_4$ requires C, 63·7; H, 8·0%; equiv., 113). The m. p. depends very much on the rate of heating. This acid was saturated to tetranitromethane, to the Liebermann–Burchard reagent, and to potassium permanganate. It showed no absorption in the ultra-violet even in the range 195—215 mμ.

On melting, the $C_{13}H_{18}O_4$ dicarboxylic acid afforded, after decomposition was complete, its *anhydride*. This was purified by recrystallisation from cold light petroleum and formed beautiful needles, m. p. 42°, $[\alpha]_D$ −71° (*c*, 1·06) (Found : C, 69·0; H, 7·6%; equiv., 105, 104, 105·5. $C_{13}H_{16}O_3$ requires C, 69·2; H, 7·75%; equiv., 104). For the determination of the equivalent the anhydride was boiled with water before being titrated; in model experiments it was shown that this regenerated the dicarboxylic acid.

The $C_{13}H_{18}O_4$ dicarboxylic acid could also be prepared by boiling its precursor with concentrated nitric acid (16 ml. per g. of diketone) for 2 hours. Dilution with water, refluxing to hydrate the anhydride initially formed, and cooling gave the $C_{13}H_{18}O_4$ dicarboxylic acid (5·5 g. from 9 g. of crude diketone).

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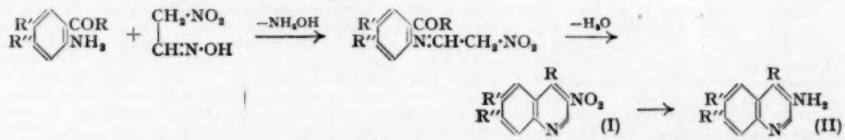
664. *Reactions of Methazonic Acid. Part II.* Some 3-Aminolepidines, 3-Amino-4-arylquinolines, and Derived Compounds.*

By K. Schofield and R. S. Theobald.

Several 3-aminolepidines and 3-amino-4-arylquinolines have been prepared by reducing the related 3-nitroquinolines described in Part I (*loc. cit.*). 3-Aminolepidine on diazotisation and treatment with pyridine gives two isomeric 3-pyridyl-lepidines. 3-Amino-4-phenyl- and 3-amino-4-*p*-methoxyphenyl-quinoline have been deaminated to 4-phenyl- and 4-*p*-methoxyphenyl-quinoline. 3-Benzamido-4-phenylquinoline is converted by phosphoric oxide into 2-phenyl-3 : 4-5 : 6-dibenzo-1 : 7-naphthyridine, the quaternisation of which is reported.

Our aim in the present work was to utilise the 3-nitrolepidines (I; R = Me) and 4-aryl-3-nitroquinolines (I; R = Ar), prepared from methazonic acid and various ketones as described in Part I (*loc. cit.*) and illustrated below, as sources of 3-amino-compounds required for various syntheses. The inability of one of us to continue this work makes it desirable to report the results so far obtained, though they are incomplete.



As a group, 3-aminoquinolines have hitherto most frequently been prepared by methods other than the reduction of 3-nitroquinolines. Practicable methods reported in the literature have involved Hofmann or Curtius reactions with quinoline-3-carboxylic acids (Mills and Watson, *J.*, 1910, **97**, 741; Lawson, Perkin, and Robinson, *J.*, 1924, **125**, 626; Wojahn and Kramer, *Arch. Pharm.*, 1938, **276**, 291), direct replacement of the 3-hydroxyl group (G.P. 611,691, 630,769; F.P. 789,068; B.P. 448,502; U.S.PP. 2,077,903, 2,098,927) and of the 3-bromo-atom (Jansen and Wibaut, *Rec. Trav. chim.*, 1937, **56**, 709; Renshaw and Friedman, *J. Amer. Chem. Soc.*, 1939, **61**, 3320), and direct synthesis (Berlingozzi *et al.*, *Gazzetta*, 1923, **53**, 3, 369; *Atti R. Accad. Lincei*, 1923, **32**, 403; *Ann. Chim. appl.*, 1927, **17**, 250; Petrow, Stack, and Wragg, *J.*, 1943, 316). In reported preparations of 3-aminoquinolines by reduction of the nitro-compounds, the reagents used have been tin and hydrochloric acid (Bergellini and Settimj, *Gazzetta*, 1923, **53**, 601), stannous chloride (Musajo, *ibid.*, 1937, **67**, 222), iron and acetic acid (Colonna, *Boll. sci. Facoltà Chim. Ind. Bologna*, 1941, 89), sodium sulphite and hydrochloric acid, and hydrogen with Adams's catalyst (Clemo and Swan, *J.*, 1945, 867).

Several of the 3-nitrolepidines previously described (Part I, *loc. cit.*) have now been reduced on the small scale by means of stannous chloride and hydrochloric acid. In this way satisfactory yields of 3-aminolepidine (II; R = Me, R′ = R″ = H), 3-amino-6- and -7-chlorolepidine (II; R = Me, R′ = Cl or H, R″ = H or Cl), and 3-amino-4 : 6 : 7-trimethylquinoline (II; R = R′ = R″ = Me) were obtained. Likewise, 3-amino-6 : 7-*cyclo*penteno- and 3-amino-6 : 7-*cyclo*hexeno-lepidine (II; R = Me, R′R″ = $[CH_2]_3$ or $[CH_2]_4$) were prepared, but 3 : 6-dinitrolepidine (I; R = Me, R′ = NO_2, R″ = H) gave only a small yield of an unidentified amino-nitrolepidine.

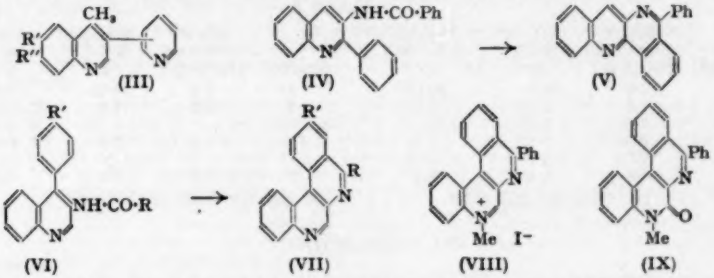
The same reagents were also found convenient for the reduction of 4-aryl-3-nitroquinolines, leading to 3-amino-4-phenyl-, -4-*p*-methoxyphenyl-, and -4-2′-pyridyl-quinoline (II; R′ = R″ = H, R = Ph, *p*-MeO·C_6H_4, or 2′-C_5H_4N, respectively).

Fluorescence in acid solution appears to be a fairly widespread property of 3-aminoquinolines, and Stark (*Ber.*, 1907, **40**, 3434) has reported the use of 3-aminoquinaldine as a fluorescence indicator in certain titrations. 3-Aminolepidine also exhibits a feeble violet fluorescence in dilute acid solution, but outstanding among the new derivatives was 3-amino-7-chlorolepidine, which showed marked blue fluorescence in both dilute acid and alcoholic solution. Equally powerful was that exhibited by 3-amino-4-phenylquinoline in alcohol, but its 4-*p*-methoxyphenyl analogue

* Part I, *J.*, 1950, 395.

was much less effective, and 3-amino-4-2′-pyridylquinoline did not fluoresce. It also seems to be a characteristic tendency of these new derivatives to retain water, even after drying *in vacuo*.

In view of the work of Coates, Cook, *et al.* (*J.*, 1943, 401), which revealed pronounced antispasmodic activity in 3-pyridylquinolines, we envisaged the preparation of the related 3-pyridyllepidines (III) from the above-described amines. Preliminary experiments showed that two isomeric 3-pyridyl-lepidines, isolated as their dipicrates, were formed from diazotised 3-amino-



(III) (IV) (V) (VI) (VII) (VIII) (IX)

lepidine and pyridine. It is of interest that these compounds form dipicrates. The complicated pattern of picrate formation shown by the experiments of Coates *et al.* (*loc. cit.*) and of Hey and Williams (*J.*, 1950, 1678) in the cases of pyridylquinolines, 4-pyridylquinaldines, and 2-pyridyl-lepidines makes it unwise, however, to draw conclusions on this basis about the compounds now described. Their orientations are being examined.

The deamination of 3-amino-4-arylquinolines appeared to offer a route, possibly superior in some cases to those already available, for the preparation of 4-arylquinolines. The action of hypophosphorous acid on diazotised 3-amino-4-phenyl- and 3-amino-4-*p*-methoxyphenyl-quinoline gave moderate yields of 4-phenyl- and 4-*p*-methoxyphenyl-quinoline, isolated as picrates. Similarly, 3-amino-4-2′-pyridylquinoline was converted into 4-2′-pyridylquinoline picrate, which completes the series of isomeric 4-pyridylquinolines (see Hey and Williams, *loc. cit.*).

Recently, Petrow, Stack, and Wragg (*loc. cit.*), by dehydration of 3-benzamido-2-phenylquinoline (IV) with phosphoric oxide, were able to synthesise the 3 : 4-6 : 7-dibenzo-1 : 5-naphthyridine derivative (V), but found 3-*p*-nitrobenzamido-2-phenylquinoline to be resinified by this treatment. From the acetamido-compound was obtained a product which despite fairly satisfactory analytical evidence was not formulated as a dibenzonaphthyridine. The application of similar cyclisations to 3-acylamino-4-arylquinolines (VI) was of interest because of the possible formation of derivatives of 3 : 4-5 : 6-dibenzo-1 : 7-naphthyridine (VII), a ring-system hitherto unknown and related to 3 : 4-benzophenanthrene. 3-Benzamido-4-phenylquinoline (VI; R = Ph, R′ = H) was in fact converted by phosphoric oxide at 270—280° into 2-phenyl-3 : 4-5 : 6-dibenzo-1 : 7-naphthyridine (VII; R = Ph, R′ = H). 3-Acetamido-4-phenylquinoline (VI; R = Me, R′ = H) was decomposed under these conditions, and the same reagent resinified 3-benzamido- and 3-acetamido-4-*p*-methoxyphenylquinoline (VI; R = Ph or Me, R′ = OMe). The milder reagent, phosphorus oxychloride, used so successfully in the Morgan–Walls phenanthridine synthesis (*J.*, 1931, 2447; 1938, 389), proved ineffective in these cases, causing decomposition of both acetamido-compounds and the conversion of 3-benzamido-4-*p*-methoxyphenylquinoline into a good yield of an unidentified substance, possibly $C_{16}H_{12}O_2N$, which we are examining.

In view of the relation of the system (VII) to phenanthridine trypanocides (Walls, *J. Soc. Chem. Ind.*, 1947, **66**, 182), we quaternised 2-phenyl-3 : 4-5 : 6-dibenzo-1 : 7-naphthyridine with methyl sulphate, and converted the product into the methiodide. The latter substance, initially yellow, was converted by recrystallisation into lustrous black crystals of the compound (VIII). These changes may be due to polymorphism, or to variations in the degree of hydration of the product. Oxidation of this compound with alkaline potassium ferricyanide gave a product which gave an analysis in fairly satisfactory agreement with that for (IX). Such a compound could clearly not have been formed, except by the elimination of the phenyl group, had quaternisation occurred on the alternative nitrogen atom.

These various lines of work are being actively pursued.

Experimental.

(M. p.s are uncorrected.)

3-*Aminolepidines and* 3-*Amino-4-arylquinolines*.—These compounds were prepared by heating the quantities of materials stated below for 1 hour at 95°, making the mixture strongly alkaline with sodium hydroxide solution, and extracting the products with ether or chloroform. The new products are tabulated in Table I, their numbers being as in Table II.

Table I.

Product	Wt. of nitro-compound (g.)	Wt. of $SnCl_2$ (g.)	Vol. of conc. HCl (c.c.)	Product	Wt. of nitro-compound (g.)	Wt. of $SnCl_2$ (g.)	Vol. of conc. HCl (c.c.)
1	3·0	10·8	30 (*a*)	7	0·2	0·58	3 (*b*)
2	0·5	1·53	10 (*b*)	8	3·2	9·0	30, and 30 c.c. of AcOH (*a*)
3	0·6	1·83	5 ,,				
4	0·35	1·12	5 ,,	9	1·0	2·8	15, and 5 c.c. of AcOH (*b*)
5	0·25	0·75	3 ,,				
6	0·5	1·4	5 ,,	10	0·5	1·4	5 (*b*)

(*a*) Extracted with ether. (*b*) Extracted with chloroform.

Table II.

	Compound R	R′	R″	Yield, % *	Crystalline form †	M. p.	Formula	Analysis: Found C	Found H	Calc. C	Calc. H
1	Me	H	H	79	Dense pale yellow prisms	72—73°	$C_{10}H_{10}N_2,H_2O$	69·3	6·9	68·2	6·9
2	,,	Cl	,,	100	Lustreless fawn needles	189—190	$C_{10}H_9N_2Cl$	61·9	4·6	62·3	4·7
3	,,	H	Cl	80	Colourless leaflets	129—130	,,	62·7	4·7	,,	,,
4	,,	Me	Me	89	Cream needles	152—153	$C_{12}H_{14}N_2,\frac{1}{2}H_2O$	74·7	7·0	74·9	6·5
5	,,	·$[CH_2]_3$·		46	Lustreless cream plates	190—191	$C_{13}H_{14}N_2$	78·1	7·1	78·7	7·1
6	,,	·$[CH_2]_4$·		57	White needles	97—98	$C_{14}H_{18}N_2,\frac{1}{2}H_2O$	76·8	7·4	77·0	8·2
7	,,	NO_2 or H	H or NO_2	Very small	Orange crystals	241 *	$C_{10}H_9O_2N_3$	59·5	5·0	59·1	4·5
8	Ph	H	H	82	Colourless needles	127—128	$C_{15}H_{12}N_2,\frac{1}{2}H_2O$	80·4	5·75	80·2	5·6
9	*p*-MeO·C_6H_4	H	H	61	Colourless needles	199—200	$C_{14}H_{14}ON_2$	76·4	5·7	76·8	6·0
10	2′-C_5H_4N	H	H	100	Fawn prisms	143—144	$C_{14}H_{11}N_3$	75·9	5·0	75·9	5·0

* Of once crystallised product.
† Alcohol was the solvent for 9, aqueous alcohol in other cases.
* With decomposition.

3-Amino-4-phenylquinoline, when treated with acetic anhydride at 95°, gave 3-*acetamido*-4-*phenylquinoline*, which formed needles, m. p. 168—169°, from dilute alcohol (Found: C, 77·6; H, 5·3; N, 10·8. $C_{17}H_{14}ON_2$ requires C, 77·8; H, 5·4; N, 10·7%). Benzoylation was effected in pyridine with benzoyl chloride for 12 hours at room temperature. 3-*Benzamido*-4-*phenylquinoline* gave leaflets, m. p. 164—165°, from dilute ethanol (Found: C, 81·0; H, 4·9; N, 7·9. $C_{22}H_{16}ON_2$ requires C, 81·45; H, 5·0; N, 8·6%).

3-*Acetamido*- [leaflets, m. p. 146—147°, from aqueous alcohol (Found: C, 74·0; H, 5·5. $C_{14}H_{16}O_2N_2$ requires C, 73·9; H, 5·5%)] and 3-*benzamido*-4-p-*methoxyphenylquinoline* [needles, m. p. 182—183°, from the same solvent (Found: C, 77·25; H, 4·9. $C_{23}H_{18}O_2N_2$ requires C, 77·9; H, 5·1%)] were prepared similarly.

3-*Pyridyl-lepidines*.—The hydrochloride suspension from 3-aminolepidine (0·5 g.), concentrated hydrochloric acid (5 c.c.), and water (2 c.c.) was diazotised † at 0° with sodium nitrite (0·22 g.) in water (2 c.c.). The violet solution was diluted with iced water (20 c.c.) and added gradually to pyridine (25 c.c.) at 50°. After remaining overnight at room temperature, the pyridine was removed in steam, and the residual tar extracted with boiling benzene. The aqueous layer was also extracted with benzene, and the combined extracts were dried (Na_2CO_3) and concentrated. Treatment of the residual oil (0·35 g.) in ethanol (5 c.c.) with picric acid (1 g.) in the same solvent (10 c.c.) gave a precipitate of mixed picrates (0·62 g.; m. p. 167—176°). Crystallisation from acetone (15 c.c.) afforded a fairly pure *dipicrate* (0·27 g.), m. p. 259—260°. This, on recrystallisation, formed small yellowish-brown leaflets, m. p. 267—268° (Found: C, 48·0; H, 2·5. $C_{15}H_{12}N_2,2C_6H_3O_7N_3$ requires C, 47·8; H, 2·7%). The original acetone liquor, on addition of ethanol (10 c.c.) and concentration to 10 c.c., deposited the second

† Further experiments, to be described later, have shown this diazotisation to be complicated.

isomer [0·12 g.; m. p. 173—178° (decomp.)]. This more soluble *dipicrate* formed clusters of yellowish-brown needles, m. p. 194—195° (Found: C, 49·6; H, 3·1%), from alcohol.

4-Phenylquinoline.—A solution of 3-amino-4-phenylquinoline (0·5 g.) in concentrated hydrochloric acid (2 c.c.) and water (3 c.c.) was diazotised at 0° with sodium nitrite (0·15 g.) in water (1 c.c.), and treated with an ice-cold solution of hypophosphorus acid (4 c.c.; 15%). After 12 hours at 0° the solution was basified with sodium hydroxide solution and extracted with ether. The dried (Na_2CO_3) extract yielded an oil (0·36 g.) which did not crystallise. This was treated in alcohol with picric acid, and the crude precipitate (0·58 g.; m. p. 218—220°) recrystallised from alcohol; it formed fine yellow needles, m. p. 224—225° (Found: C, 57·9; H, 3·1. Calc. for $C_{15}H_{11}N,C_6H_3O_7N_3$: C, 58·1; H, 3·25%). Kenner and Statham (*J.*, 1935, 299) give m. p. 225°.

In a further experiment on the same scale, the basified reaction mixture was steam-distilled. Ether extraction of the distillate gave 4-phenylquinoline (0·19 g.), which slowly crystallised from ether–light petroleum (b. p. 40—60°) in colourless needles, m. p. 59—61°. Koenigs and Nef (*Ber.*, 1886, **19**, 2427) give m. p. 61—62°.

4-p-Methoxyphenylquinoline.—3-Amino-4-*p*-methoxyphenylquinoline (1 g.) in concentrated hydrochloric acid (2 c.c.) and water (3 c.c.) was diazotised at 0° with sodium nitrite (0·28 g.) in water (2 c.c.). The precipitated diazonium salt was redissolved by addition of iced water (20 c.c.) and hypophosphorous acid (3·5 c.c.; 30%), and after 24 hours at 0° the mixture was basified and extracted with ether. The oily residue (0·86 g.) from concentration of the dried (Na_2CO_3) extract was converted into crude 4-*p*-methoxyphenylquinoline picrate (1·02 g.), which crystallised from alcohol in reddish-brown crystals, m. p. 234—235° (Found: C, 57·9; H, 3·6. Calc. for $C_{16}H_{13}ON,C_6H_3O_7N_3$: C, 56·9; H, 3·5%). Kenner and Statham (*loc. cit.*), give m. p. 232—234° (decomp.). The free base, which was not analysed, was obtained by decomposition of the picrate with sodium hydroxide solution. It formed leaflets, m. p. 82—83°, from light petroleum (b. p. 40—60°).

4-2'-Pyridylquinoline Picrate.—3-Amino-4-2'-pyridylquinoline (0·1 g.) in concentrated hydrochloric acid (1 c.c.) and water (2 c.c.) was diazotised at 0° with sodium nitrite (0·04 g.) in water (1 c.c.), and the solution was treated with hypophosphorous acid (2 c.c.; 30%). After 12 hours at 0° the solution was made alkaline with sodium hydroxide solution and extracted with ether, giving on concentration an oil (0·11 g.) which did not crystallise. The *picrate* (0·06 g.; m. p. 197—200°), formed in alcoholic solution, separated from ethanol as a pale yellow solid, m. p. 199—200° (Found: C, 56·2; H, 3·5. $C_{14}H_{10}N_2,C_6H_3O_7N_3$ requires C, 55·2; H, 3·0%).

2-Phenyl-3 : 4-5 : 6-dibenzo-1 : 7-naphthyridine and its Quaternisation.—An intimate mixture of 3-benzamido-4-phenylquinoline (0·1 g.) and phosphoric oxide (2 g.) was kept at 270—280° for 2 hours and then treated with ice, and the grey solid was collected and extracted with acetone–concentrated ammonia solution (3 : 1 by vol.). Concentration of the extract afforded silky needles (0·05 g., m. p. 154—155°). The pure *naphthyridine*, after crystallisation from dilute aqueous alcohol, melted at 157—158° (Found: C, 85·9; H, 4·5; N, 9·5. $C_{22}H_{14}N_2$ requires C, 86·3; H, 4·6; N, 9·15%).

The above compound (0·2 g.) and methyl sulphate (0·08 g.) were heated under reflux in benzene (10 c.c.) for 2 hours, the solvent was evaporated, and the residual gum dissolved in hot water (25 c.c.). Addition of potassium iodide solution precipitated the methiodide [0·25 g.; m. p. 232—235° (decomp.)] as a flocculent yellow solid which crystallised from ethanol (20 c.c.) in orange-yellow needles (0·19 g.), m. p. 234—235° (decomp.). In subsequent crystallisations from ethanol the compound separated as orange-yellow needles, golden leaflets, and finally as black needles with a golden reflex. When heated the last turned yellow at 143° and melted at 231—232° (decomp.) (Found: C, 56·4; H, 3·9. $C_{23}H_{17}N_2I,2H_2O$ requires C, 56·9; H, 4·4%).

Oxidation of the quaternary salt (0·1 g.) with potassium ferricyanide (0·3 g.), water (25 c.c.), and 2N-sodium hydroxide solution (10 c.c.) at 95° for 1 hour with stirring, followed by extraction with benzene, provided a solid (0·03 g.), m. p. 123—128°. The *substance* separated from benzene–ligroin (b. p. 60—80°) as small fawn needles, m. p. 135—137° (decomp.) (Found: C, 83·5; H, 5·5. $C_{23}H_{16}ON_2$ requires C, 82·1; H, 4·8%).

Attempted Cyclisation of 3-Benzamido-4-p-methoxyphenylquinoline.—The benzamido-compound (2 g.) and phosphorus oxychloride (20 c.c.) were heated under reflux for 30 hours, and the mixture was decomposed with ice and basified with ammonia solution. Crystallisation of the solid (1·3 g.) from dilute alcohol gave fine needles of a *substance*, m. p. 118—119° (Found: C, 75·8, 76·2; H, 5·25, 5·2; N, 4·1, 6·3. $C_{14}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%).

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WASHINGTON SINGER LABORATORIES,
PRINCE OF WALES ROAD, EXETER.

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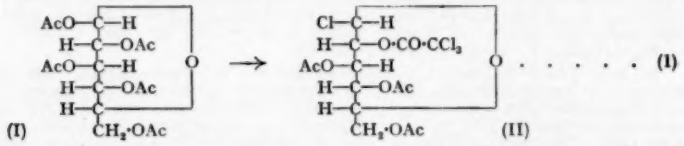
665. *The Chlorination of β-D-Glucopyranose Penta-acetate. Abnormal Reactions of Phosphorus Pentachloride.*

By R. A. Abramovitch.

The reaction of phosphorus pentachloride with β-D-glucopyranose penta-acetate, to give 3 : 4 : 6-triacetyl 2-trichloroacetyl β-D-glucosyl chloride, is assumed to proceed according to two mechanisms: the normal replacement of acetyl at $C_{(1)}$, and abnormal substitution into the 2-acetyl group. It it suggested that the latter follows dissociation of the phosphorus pentachloride, the chlorine thus obtained then acting as a substituting agent, probably catalysed by the acetyl chloride also present. The action of thionyl chloride and of phosphorus trichloride on β-D-glucopyranose is described.

3 : 4 : 6-Triacetyl 2-trichloroacetyl β-D-glucosyl chloride (II) is obtained from β-D-glucopyranose penta-acetate (I) by the action of phosphorus pentachloride (Brigl, *Z. physiol. Chem.*, 1921, **116**, 1; Hickinbottom, *J.*, 1929, 1676). The structure of (II) is beyond doubt because hydrolysis with ammonia in dry ether gave trichloroacetamide and 3 : 4 : 6-triacetyl β-glucosyl chloride which with sulphuryl chloride yielded the 2-chlorosulphonate and with phosphorus pentachloride yielded the 2-chloro-derivative (Brigl, *loc. cit.*).



Reaction (1) presents two striking points: (i) Phosphorus pentachloride appears to react by two different mechanisms: first, replacement of the 1-acetyl group by chlorine, yielding phosphorus oxychloride and acetyl chloride as by-products; secondly, the abnormal chlorination of the 2-acetyl group. (ii) Only the 2-acetyl group appears to be attacked. The latter fact may be related to the configuration at $C_{(2)}$, and the reactions of the corresponding mannose and galactose derivatives are being examined. The halogen in position 1 may also favour the substitution by its *-I* effect, although this involves the assumptions that reaction at the 1-position precedes chlorination and that the influence would be sufficiently powerful to make itself felt along the rather long –C–C–O–C–C– chain. The low maximum yield (45%) suggests that other substitution products are also formed but examination of the final oil had negative results.

Chlorination by phosphorus pentachloride should lead to phosphorus trichloride as an end-product, and this was isolated in good yield from the reaction mixture. The pentachloride as such has no chlorinating action; this presumably arises by dissociation, $PCl_5 \rightleftharpoons PCl_3 + Cl_2$, which according to Smith and Lombard (*J. Amer. Chem. Soc.*, 1915, **37**, 2060) occurs to an appreciable extent under the reaction conditions used in the present work. The chlorinating action of chlorine on acids, and thus presumably on the acetoxy-group, is catalysed by acid chlorides, as in the Hell–Volhard reaction (cf. Watson and Roberts, *J.*, 1928, 2779; Watson and Gregory, *J.*, 1929, 1373).

The isolation of phosphorus trichloride favours this hypothesis, and it has been found that β-D-glucopyranose penta-acetate is unaffected by the trichloride. Further, removal of the catalysts (phosphorus trichloride and acetyl chloride) from the reaction mixture by conducting the reaction without a reflux condensor very greatly reduced the formation of trichloroacetyl derivative, whereas addition of a little acetyl chloride before or during the reaction accelerates it (although it does not affect the yield).

Finally, thionyl chloride, which resembles phosphorus pentachloride except that it does not dissociate to yield chlorine under the reaction conditions under consideration (Schenk, *Z. anorg. Chem.*, 1937, **233**, 385), does not afford any trichloroacetyl derivative from the glucose penta-acetate: it affords α-acetochloroglucose (with inversion) and an oil which also affords

tetra-acetyl methyl-α-D-glucoside on treatment with methanol and silver carbonate, and is probably a modified β-acetochloroglucose.

"Abnormal" (chlorinating) actions by phosphorus pentachloride have already been recorded in various cases. An excess of the boiling reagent slowly chlorinates acetyl chloride (Michael, *J. pr. Chem.*, 1887, **35**, 95; Friederici, *Ber.*, 1878, **11**, 1971), and with chloroacetic acid yields tetrachloroethylene and, probably, tetra- and penta-chloroethane (Michael, *loc. cit.*). Trichlorovinyl phenyl ether is obtained from phenyl acetate, resorcinol bistrichloroacetyl ether from resorcinol diacetate, and 1 : 2-dichlorobut-1-enyl phenyl ether from phenyl propionate (*idem*, *loc. cit.*). A possible mechanism for the formation of the chlorovinyl derivatives is exemplified by the following scheme for the formation of tetrachloroethylene :

$$CH_2Cl{\cdot}CO_2H + PCl_5 \longrightarrow CH_2Cl{\cdot}COCl$$
$$CH_2Cl{\cdot}COCl + PCl_5 \longrightarrow CH_2Cl{\cdot}CCl_3$$
$$PCl_5 \rightleftharpoons PCl_3 + Cl_2$$
$$CH_2Cl{\cdot}CCl_3 + Cl_2 \longrightarrow [CHCl_2{\cdot}CCl_3] \longrightarrow CCl_2{:}CCl_2$$

Again, it is well known that phosphorus pentachloride reacts with many aldehydes and ketones. If the hydrocarbon radicals are simple, replacement of oxygen by chlorine takes place (*e.g.*, $COMe_2 \longrightarrow CMe_2Cl_2$). Frequently unsaturated monochloro-compounds, apparently formed by the loss of hydrogen chloride from the expected dichloro-compounds, are found among the products (cf. above). If the hydrocarbon radicals are complex, the pentachloride sometimes replaces an α-hydrogen atom and a chloro-ketone results (*e.g.*, $COPr^i_2 \longrightarrow Pr^i{\cdot}CO{\cdot}CMe_2Cl$). An excess of the halide has no effect on the carbonyl group (Gilman, "Organic Chemistry," Vol. I, p. 665). This suggests that the hydrocarbon radical is the influencing factor only insofar as the boiling point of the ketone increases with the complexity of the radical, so that the higher is the temperature of the boiling mixture the greater is the dissociation of phosphorus pentachloride. This is supported by the fact that phosphorus pentabromide dissociates more readily than the pentachloride and gives the α-bromo-compound in all cases (Gilman, *op. cit.*). This explanation is more suitable than that which assumes that the reactivity of the carbonyl group is affected by the attached hydrocarbon residues so considerably as to alter the course of the reaction.

Experimental.

All m. p.s are uncorrected.

For the chlorine determinations, advantage was taken of the easily hydrolysable nature of the compounds. Before carrying out the determinations, the method was checked on the known α-acetobromoglucose, twice recrystallised from *n*-amyl alcohol (Found : Br, 19·1. Calc. for $C_{14}H_{19}O_9Br$: Br, 19·45%).

A known weight of the compound was dissolved in methanol (free from halogen), and ~2N-sodium hydroxide (AnalaR) methanol–water (1 : 1; v/v) was added. The whole was shaken occasionally during 2 days, after which the solution was exactly neutralized with nitric acid (AnalaR) to phenolphthalein. The solution thus obtained was rapidly titrated against standard silver nitrate (Mohr's method).

The acetyl groups were determined by hydrolysis with standard alkali (back-titration of the excess).

β-Penta-acetyl Glucose.—The method given by Vogel ("Practical organic chemistry," 1st edn., p. 439) was used. In all the following reactions, the crude compound, dried on a porous plate for about a month was found to be suitable.

3 : 4 : 6-*Triacetyl* 2-*Trichloroacetyl* β-*Glucosyl Chloride.*—(*a*) β-Penta-acetyl glucose (39 g.) and phosphorus pentachloride (104 g.) were heated on the water-bath under reflux (calcium chloride guard-tube), the mixture soon becoming liquid. Heating was continued till the evolution of hydrogen chloride was complete (2·5 hours). The liquid was distilled in a vacuum first at about 50°, then at 100° for a short period. The distillate (A) was collected. The residue was allowed to cool, covered with sodium-dried ether (50 ml.), shaken vigorously, and set aside, preferably in the ice-box. The crystals were filtered off and washed with a small amount of dry ether, and the filtrate (B) was put aside. The solid was washed with ice-cold methanol (25 ml.) and recrystallized from dry ether, yielding long white needles (14 g.), m. p. 140° (Brigl, *loc. cit.*, gives 142°).

These on hydrolysis with ammonia in dry ether gave 3 : 4 : 6-triacetyl β-glucosyl chloride, m. p. 156—158° (Brigl, *loc. cit.*; Winslow, Thesis, 1947).

(*b*) The preparation was carried out without a reflux condenser but using a calcium chloride guard tube. After 2·5 hours a dark brown oil remained. Occasionally, tar formation took place. The oil

was covered with a small amount of ether and shaken as before, then set aside. A very small amount of crystals appeared overnight, and these were treated as before.

In one case, acetyl chloride (10 c.c.) was added to the β-penta-acetyl glucose, and then phosphorus pentachloride was added. An uncontrollable reaction set in at once at room temperature and when it subsided a dark brown tar was left. When acetyl chloride was added through the condenser after the addition of phosphorus pentachloride, the reaction was complete in less than 2 hours.

Fractionation of the vacuum-distillate (*A*). Fractionation of (A) gave fractions: (i) b. p. 52—58°, (ii) b. p. 75—77°, and (iii) b. p. 106—107°. Refractionation of each showed (i) to be acetyl chloride, b. p. 55°, (ii) to be phosphorus trichloride, b. p. 76°, *d* 1·613, and (iii) to be phosphorus oxychloride, b. p. 107°. These were obtained in the approx. molecular ratio of 1 : 3 : 1.

Examination of the filtrate (*B*). The oil was poured with vigorous stirring into ice-water, extracted with ether, washed with dilute sodium hydrogen carbonate solution, then again with water, and dried ($CaCl_2$). The ether was removed and the oil left extracted with light petroleum (b. p. 60—80°). Decantation and cooling yielded fine needles, m. p. 130—133°, recrystallizing from dry ether as long needles, m. p. 140° undepressed when mixed with an original sample of 3 : 4 : 6-triacetyl 2-trichloroacetyl β-glucosyl chloride (Found: Cl, 30·0. Calc. for $C_{14}H_{19}O_9Cl$: Cl, 30·2%). The total yield after repeated extraction was 3 g.

The small amount of oil left was dissolved in methanol (40 ml.) and freshly prepared silver carbonate (2 g.) was added. The whole was shaken occasionally for 24 hours. Filtration and evaporation gave only an unidentified white oil.

Action of Phosphorus Trichloride on β-Penta-acetyl Glucose.—To β-penta-acetyl glucose (40 g.) was added phosphorus trichloride (44 c.c.), and the mixture was refluxed. The solid penta-acetate dissolved but the whole set to a solid mass on cooling. After 2·5 hours' boiling, the liquid fraction was distilled off at atmospheric pressure and was found to be unchanged trichloride (42 c.c., 95·4%). The solid, washed with ice–water and recrystallized from methyl, ethyl, or amyl alcohol or ether, had m. p. 130°, undepressed when mixed with authentic specimens of β-penta-acetyl glucose (Found: Ac, 54·9. Calc. for $C_{16}H_{22}O_{11}$: Ac, 55·1%). The amount of solid recovered after the reaction was almost 99%. The same result was obtained when the mixture was refluxed for 4 hours.

Action of Thionyl Chloride on β-Penta-acetyl Glucose.—To β-penta-acetyl glucose (39 g.), redistilled thionyl chloride (67 g.) was added. The mixture was then heated for 2·5 hours on the water-bath. Excess of thionyl chloride was removed in a vacuum, and the residue cooled, shaken with dry ether (50 c.c.), and set aside overnight. Only a small amount of dark impurities separated. The filtrate was diluted with ether, washed successively with ice-water, dilute sodium hydrogen carbonate solution, and water, and dried ($CaCl_2$). The ether was evaporated off and a yellowish brown oil was left. This was extracted with boiling light petroleum (b. p. 40—60°), and the hot supernatant liquid decanted. On cooling, a white oil (C) settled out. The clear, cold solution was decanted, scratched and set aside. Fine needle-like crystals appeared (2·6 g.) which were filtered off and dried (vacuum; soda-lime–phosphoric oxide) (m. p. 63—65°). These, after two recrystallizations from light petroleum (b. p. 40—50°), melted at 73° alone or mixed with α-acetochloroglucose (Found: Cl, 9·2. Calc. for $C_{14}H_{19}O_9Cl$: Cl, 9·7%). Dissolution in cold methanol, addition of silver carbonate, shaking occasionally during 24 hours, then filtration, evaporation, and crystallization from aqueous alcohol, gave tetra-acetyl methyl-β-D-glucoside, as long white needles, m. p. 105—106°. The oil (C) gave, on similar treatment, tetra-acetyl methyl-α-D-glucoside as needles, m. p. 100—101°. The initial crystals, m. p. 63—65°, were probably a mixture of the α- and the β-form, preponderating by the α-form. The total yield of α-acetochloroglucose after repeated extraction was 5 g., and of β-acetochloroglucose (calculated from the tetra-acetyl methylglucoside) 3 g. The pale brown oil left after complete extraction of acetochloroglucose could not be characterised by its methylglucoside since extensive hydrolysis occurred (Fehling's solution reduced easily), and only a small yield of a high-melting powder was obtained.

The author thanks Mr. L. Marchal, Headmaster of the Lycée Français, Alexandria, in whose laboratory this work was carried out. He is also greatly indebted to Prof. J. Kenyon for valuable discussions, suggestions, and encouragement.

FAROUK IST UNIVERSITY, ALEXANDRIA, EGYPT. [*Received, July 13th*, 1951.]

666. *Oxidation of Organic Compounds by Nitrous Oxide. Part 1.**

By F. S. Bridson-Jones, G. D. Buckley, L. H. Cross, and A. P. Driver.

Nitrous oxide fails to react with most types of organic compound at 200—350° and pressures up to 2000 atm., but oxidises benzaldehyde to benzoic acid, and certain secondary aromatic alcohols to the corresponding ketones.

Olefins are readily oxidised to carbonyl compounds, the reactions being of three types :

(i) Oxidation at the double bond to give a carbonyl compound containing the same number of carbon atoms as the original olefin.

$$CR^1R^2{=}CR^3R^4 + N_2O \longrightarrow CR^1R^2R^3{\cdot}CO{\cdot}R^4 + N_2$$

(ii) Oxidative fission at the double bond to give two carbonyl compounds.

$$CR^1R^2{=}CR^3R^4 + 2N_2O \longrightarrow CR^1R^2{=}O + CR^3R^4{=}O + 2N_2$$

(iii) Reaction of two molecules of the olefin with one molecule of nitrous oxide to give one molecule of a carbonyl compound and one molecule of a *cyclo*propane derivative.

$$2CR^1R^2{=}CR^3R^4 + N_2O \longrightarrow CR^1R^2{=}O + R^1R^2C\begin{array}{l}\diagup CR^3R^4\\ \diagdown CR^3R^4\end{array} + N_2$$

Ethylene, and monosubstituted and 1 : 2-disubstituted ethylenes react mainly according to reaction (i), but in many cases reactions (ii) and (iii) also occur to some extent. 1 : 1-Disubstituted ethylenes, except methylene-*cyclo*butane, react exclusively according to reaction (iii).

The initial step in the reaction of nitrous oxide with an olefin is believed to be addition of the nitrous oxide to the double bond to form a Δ^2-1 : 2 : 3-oxadiazoline which then undergoes decomposition either to give nitrogen and a carbonyl compound containing the same number of carbon atoms as the original olefin or to give an aliphatic diazo-compound and a carbonyl compound containing a smaller number of carbon atoms than the olefin. When the diazo-compound produced is diazomethane or ω-diazotoluene it reacts with a second molecule of the olefin to form a *cyclo*propane derivative, but when it is a higher diazoparaffin it reacts with a second molecule of nitrous oxide to give a carbonyl compound.

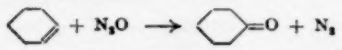
Nitrous oxide supports the combustion of hydrocarbons, ethers, and alcohols yielding nitrogen, carbon dioxide, and water, and in some cases the inflammability limits have been determined, but no attempt appears to have been made to use the gas as an agent for the controlled oxidation of organic compounds under milder conditions.

The action of nitrous oxide on a wide range of organic compounds at 200—400° and pressures up to 2000 atm. has now been studied. Under these conditions no reaction occurred with paraffins and *cyclo*paraffins (*n*-hexane, *cyclo*hexane, methyl*cyclo*hexane, methyl*cyclo*pentane), aromatic hydrocarbons (benzene, toluene, diphenylmethane, anthracene, phenanthrene), amines (aniline, dimethylaniline, triethylamine, pyridine), esters (ethyl acetate, ethyl malonate), azobenzene, deoxybenzoin, benzophenone, benzil, and furan. Acetanilide, acetylacetone, and dimedone gave tars, presumably owing largely to their own thermal instability. Of the alcohols tried, ethanol and benzyl alcohol were recovered unchanged, but benzhydrol gave a small yield of benzophenone in 4 hours at 300° and 400—500 atm., the remainder of the alcohol being recovered unchanged. Under similar conditions benzoin gave an 18% yield of benzil.

* Brief accounts of this and the succeeding two papers were presented to the International Congress of Pure and Applied Chemistry at New York, September, 1951.

Olefins, on the other hand, reacted readily with nitrous oxide at 250—300° and 100—500 atm. giving carbonyl compounds, the reactions being mainly of three types:

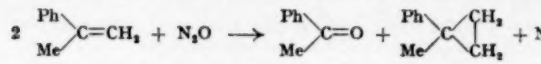
(i) Oxidation at the double bond to an aldehyde or ketone containing the same number of carbon atoms as the original olefin, *e.g.*,



(ii) Oxidative fission at the double bond to give two molecules of carbonyl compound, *e.g.*,

$$CH_3{\cdot}CH{=}CH{\cdot}CH_2{\cdot}CH_3 + 2N_2O \longrightarrow CH_3{\cdot}CHO + CH_3{\cdot}CH_2{\cdot}CHO + 2N_2$$

(iii) Reaction of two molecules of olefin with one molecule of nitrous oxide to give one molecule of a carbonyl compound and one molecule of a *cyclo*propane derivative, *e.g.*,

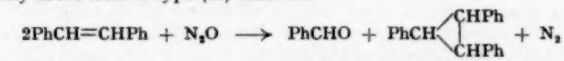


Attack was invariably at the double bond and in most cases there were no side reactions apart from self-condensation of the carbonyl compounds to give higher unsaturated bodies. Some loss of yield by this type of condensation was inevitable at the high temperatures used, especially when the primary products were aldehydes.

Ethylene, monosubstituted ethylenes, and most 1 : 2-disubstituted ethylenes reacted wholly or mainly according to reaction (i). Ethylene gave acetaldehyde together with a little crotonaldehyde and higher condensation products, but no formaldehyde. Propylene gave a mixture of acetone and propaldehyde together with their condensation products; small amounts of acetaldehyde and methyl*cyclo*propane, arising from a type (iii) reaction, were also detected, but formaldehyde was absent. Hept-1-ene similarly gave a mixture of heptanal (50%), hexanal (24%), and heptan-2-one (26%). The hexanal probably arose from a type (iii) reaction, since formaldehyde was absent from the products, although the amyl*cyclo*propane which was presumably formed in the reaction was not isolated.

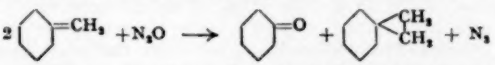
*cyclo*Hexene gave only *cyclo*hexanone, and acenaphthylene gave acenaphthenone. Pent-2-ene reacted to give 39% of pentan-2-one and 32% of pentan-3-one, together with traces of acetaldehyde and propaldehyde which arose from a type (ii) reaction; no *cyclo*propane derivatives were detected.

Stilbene behaved differently; deoxybenzoin, the product expected from reaction (i), was formed only in 20% yield, and considerable amounts of benzaldehyde, benzoic acid, and 1 : 2 : 3-triphenyl*cyclo*propane were isolated. The benzaldehyde and the triphenyl*cyclo*propane evidently arose from a type (iii) reaction.

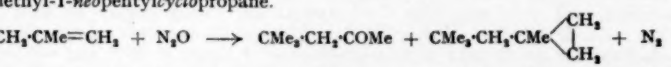


It was thought likely that the benzoic acid was formed by the further action of nitrous oxide on the benzaldehyde, and this was confirmed by the reaction of pure benzaldehyde with nitrous oxide under the conditions used for the stilbene reaction; the aldehyde was largely converted into benzoic acid.

1 : 1-Disubstituted ethylenes, with one exception, reacted exclusively according to reaction (iii), *e.g.*, methylene*cyclo*hexane gave equimolecular amounts of *cyclo*hexanone and *spiro*[2 : 5]-octane; formaldehyde was absent and no other products were detected:

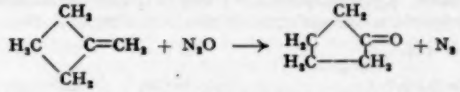


Similarly 2-phenylpropene gave a mixture of equimolecular proportions of acetophenone and 1-methyl-1-phenyl*cyclo*propane, and 2 : 4 : 4-trimethylpent-1-ene gave 4 : 4-dimethylpentan-2-one and 1-methyl-1-*neo*pentyl*cyclo*propane.



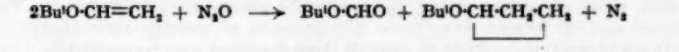
*iso*Butene gave the expected 1 : 1-dimethyl*cyclo*propane but behaved abnormally in giving a mixture of acetone and propaldehyde instead of acetone only. 1 : 1-Diphenylethylene and 1 : 1-bis-*p*-methoxyphenylethylene gave good yields of benzophenone and *pp'*-dimethoxybenzophenone respectively, but the isolation of the corresponding *cyclo*propanes in a pure

state was extremely difficult. 1 : 1-Bis-*p*-methoxyphenyl*cyclo*propane was isolated in very small yield and 1 : 1-diphenyl*cyclo*propane was not isolated at all, although the presence of a *cyclo*propane derivative was established by infra-red spectrography. The only 1 : 1-disubstituted ethylene which was examined and which failed to undergo a type (iii) reaction was methylene*cyclo*butane, which gave *cyclo*pentanone as the only identifiable product.

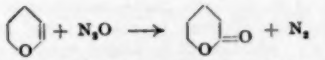


A few olefins having other types of substituent adjacent to the double bond were treated with nitrous oxide. The 1- and 2-chloropropenes gave only tars and hydrogen chloride owing to their instability under the conditions used. αβ-Unsaturated ketones failed to react with nitrous oxide, but αβ-unsaturated ethers readily gave esters.

*iso*Butyl vinyl ether reacted exclusively according to reaction (iii) giving equimolecular amounts of *iso*butyl formate and *iso*butyl *cyclo*propyl ether; no *iso*butyl acetate was detected.



On the other hand 2 : 3-dihydropyran reacted only according to reaction (i) giving δ-valerolactone in small amount.



Butyl vinyl sulphide gave a mixture of products containing oxygen, but no identifiable compound was isolated.

No evidence for the formation of olefin oxides was found in any of the reactions, although in the cases of *iso*butene and *cyclo*hexene a particularly careful search was made for evidence of their presence. It was thought possible that olefin oxides might be formed initially and then rearrange to carbonyl compounds under the conditions of the reaction. *cyclo*Hexene oxide was therefore treated with nitrous oxide at 300° and 500 atm. for 4 hours. It was however recovered unchanged.

In an attempt to find a catalyst for the reaction of nitrous oxide with olefins the effect of small amounts of Raney nickel, Raney cobalt, copper, silver, pyridine, triethylamine, sulphuric acid, acetic acid, and iodine was tried, but they all failed to bring about any increase in the rate of reaction between *cyclo*hexene and nitrous oxide.

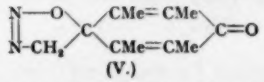
The reaction of nitrous oxide with olefins, although apparently taking very different courses in different cases, was usually quite clear-cut, giving good yields of one or two products, and attack invariably occurred at the double bond. This contrasts sharply with the oxidation of olefins by oxygen, and provides a strong argument against a free-radical mechanism. Since the oxidising action of nitrous oxide is, apart from a few special cases, a specific reaction of the double bond, since the reaction is not catalysed by iodine which is an efficient catalyst for the decomposition of nitrous oxide (Musgrave and Hinshelwood, *Proc. Roy. Soc.*, 1932, *A*, **137**, 25), and since nitrous oxide does not decompose into its elements to any appreciable extent under the conditions used, it is probable that the initial step in the reaction involves addition of the nitrous oxide molecule to the double bond.

The nitrous oxide molecule is linear, with the oxygen atom at one end, and various structures differing only in electron distribution have been formulated. Pauling (" The Nature of the Chemical Bond," Cornell University Press, 1944, pp. 126, 199) considers that the normal state of the molecule corresponds to resonance between structures (I) and (II), with minor contributions from other mesomeric forms, and spectroscopic (Plyler and Barker, *Phys. Review*, 1931, **38**, 1827) and electron-diffraction evidence (Maxwell, Mosley, and Deming, *J. Chem. Phys.*, 1934, **2**, 331) is consistent with this conclusion.

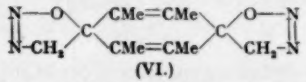
Nitrous oxide is therefore seen to be closely analogous in structure to diazomethane and phenyl azide, and like them it may be expected to add to olefinic double bonds under suitable conditions to form a 5-membered heterocyclic ring.

It is accordingly considered likely that the primary product of the reaction of nitrous oxide

with an olefin is a Δ^2-1 : 2 : 3-oxadiazoline (III). There is strong evidence that this ring system, commonly formulated as the open-chain diazonium betaine (IV), is also formed as an intermediate step in the reaction of aldehydes and ketones with aliphatic diazo-compounds (Arndt and Eistert, *Ber.*, 1935, **68**, 193), and in the reaction of β-amino-alcohols with nitrous acid (McKenzie and Richardson, *J.*, 1923, **123**, 79), and in one or two cases the 1 : 2 : 3-oxadiazolines have been isolated; *e.g.*, the spirans (V) and (VI) can be obtained in a pure state by the action of diazomethane on duroquinone (Smith and Pings, *J. Org. Chem.*, 1937, **2**, 95).



(V.)

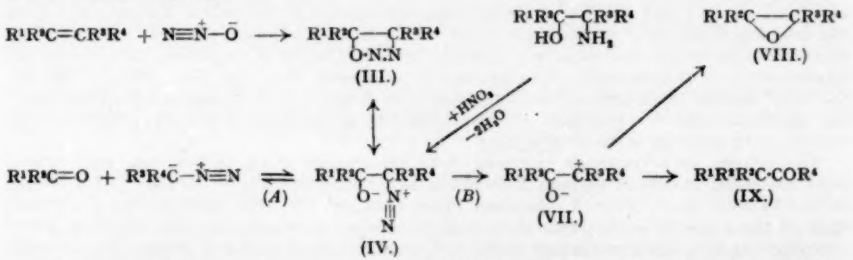


(VI.)

The 1 : 2 : 3-oxadiazolines formed by either of these two types of reaction decompose irreversibly either spontaneously or on warming, losing nitrogen to give an intermediate of type (VII), which then either cyclises to the olefin oxide (VIII) or undergoes anionotropic rearrangement to an aldehyde or ketone (IX). This breakdown of the ring will occur very rapidly under the conditions obtaining in the reaction of nitrous oxide with olefins, but it is not the only mode of decomposition which must be taken into consideration. The 1 : 2 : 3-oxadiazolines can be formed from three diverse pairs of starting materials by three very different types of reaction, and one or more of these reactions may be reversible.

The possibility of decomposition to an amino-alcohol and nitrous acid may be dismissed because in the nitrous oxide system the water required for the decomposition is absent. On the other hand, the reaction of an aliphatic diazo-compound with an aldehyde or ketone is a typical example of a nucleophilic addition to the carbonyl group, and such reactions are normally readily reversible (*e.g.*, addition of hydrogen cyanide or sodium hydrogen sulphite, the aldol reaction, etc.). This reversibility has not hitherto been detected in the addition of diazo-compounds because the addition product is rapidly and irreversibly decomposed, whereas the starting materials are relatively stable under the conditions of the reaction. But if a 1 : 2 : 3-oxadiazoline dissociates in this manner at 250—300°, the diazoparaffin formed will be rapidly removed either by thermal decomposition or by reaction with one of the other components of the reaction mixture. We may therefore conclude that the primary product of the addition of nitrous oxide to an olefin may break down either to give nitrogen and a residue (VII) which will rearrange to a carbonyl compound or an olefin oxide containing the same number of carbon atoms as the original olefin (reaction *A*), or to give a diazoparaffin and a carbonyl compound containing a smaller number of carbon atoms than the olefin (reaction *B*).

The relative importance of these two modes of decomposition will depend on the position of the equilibrium in reaction *B* and on the relative rates of reaction *A* and of the elimination of the diazoparaffin, and these factors will in turn depend largely on the number and nature of the substituent groups.



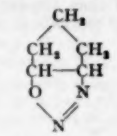
The experimental results are consistent with this interpretation. Ethylene is assumed to form Δ^2-1 : 2 : 3-oxadiazoline (III; $R^1 = R^2 = R^3 = R^4 = H$), which breaks down exclusively to nitrogen and acetaldehyde.

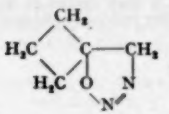
The monosubstituted ethylenes may similarly be supposed to give a mixture of the 4-substituted and the 5-substituted oxadiazoline. The 4-substituted compound (III; $R^1 = R^2 = R^3 = H$, $R^4 = R$) evidently breaks down exclusively by the *A*-type reaction to give nitrogen and the aldehyde, but the 5-substituted compound (III; $R^1 = R$, $R^2 = R^3 = R^4 = H$), although it undergoes mainly the *A*-type decomposition to nitrogen and the ketone, must also

break down to a small extent by the *B*-type reaction. The products from this reaction are an aldehyde and diazomethane, which evidently combines with unchanged olefin to give a *cyclo*propane in the known manner. In the case of *iso*butyl vinyl ether, it appears that only 5-*iso*butoxy-Δ^2-1 : 2 : 3-oxadiazoline is formed in the first step and that it then decomposes only by reaction *B*.

The 1 : 1-disubstituted ethylenes appear to give exclusively 5 : 5-disubstituted 1 : 2 : 3-oxadiazolines; the absence of formaldehyde and of aldehydes containing the same number of carbon atoms as the original olefins shows that the 4 : 4-disubstituted oxadiazolines are not formed. The former evidently undergo *B*-type decomposition only to give a ketone and diazomethane, which again reacts with the olefin to give a *cyclo*propane derivative.

Methylene*cyclo*butane is exceptional because of the instability of the 4-membered ring. It seems likely that ring expansion occurs when the olefin is attacked by nitrous oxide, with the result that 4 : 5-trimethylene-Δ^2-1 : 2 : 3-oxadiazoline (X) is formed instead of the expected 4 : 4-trimethylene-Δ^2-1 : 2 : 3-oxadiazoline (XI).

(X.) 

 (XI.)

A less plausible alternative is that (XI) is first formed and then undergoes rearrangement to (X). By analogy with the corresponding tetramethylene derivative, it is to be expected that (X) will break down exclusively according to reaction *A*.

The 1 : 2-disubstituted ethylenes will form the 4 : 5-disubstituted 1 : 2 : 3-oxadiazolines, and in the case of symmetrical olefins, *e.g.*, *cyclo*hexene and stilbene, only one oxadiazoline can be formed and hence the *A*-type decomposition produces only a single ketone. On the other hand in unsymmetrical olefins, as in pent-2-ene, two isomeric oxadiazolines and hence two isomeric ketones are formed. *B*-Type decompositions, as well as the *A*-type, apparently occur when the olefins are open-chain and result in the formation of an aldehyde R·CHO and a diazocompound R′·CHN_2. It has already been shown that diazomethane produced under these conditions reacts with the parent olefin to give a *cyclo*propane derivative. The formation of 1 : 2 : 3-triphenyl*cyclo*propane from stilbene indicates that a similar reaction occurs when R′ is aryl, but when R′ is alkyl, as in the diazoethane and 1-diazopropane which may be assumed to be formed in the fission of the oxadiazolines from pent-2-ene, the diazo-compound is apparently eliminated by reaction with nitrous oxide to form an aldehyde.

$$R'\cdot CHN_2 + N_2O \longrightarrow R'\cdot CHO + 2N_2$$

There remains one anomaly in the experimental results which is not susceptible of explanation in terms of the theory outlined above, *viz.* the formation of a small amount of propaldehyde together with the acetone in the reaction of nitrous oxide with *iso*butene, where the theory predicts the formation of acetone alone. Although this observation is as yet unaccountable it does not appear to invalidate the general thesis.

The reaction of nitrous oxide with olefins affords a simple method of preparing many carbonyl compounds and *cyclo*propane derivatives, but precautions must be taken when carrying out the reaction since nitrous oxide forms explosive mixtures with hydrocarbons. Such mixtures are liable to explode even at room temperature when compressed. Before the full extent of this hazard was properly appreciated several explosions occurred in reaction vessels, and in one case when *cyclo*hexene (25 c.c.) was being treated with nitrous oxide at 300° and 1000 atm. in a vessel of 75-c.c. capacity, capable of withstanding 5000 atm. pressure, a detonation split the vessel lengthways and destroyed the surrounding furnace. The danger was reduced by using a sufficient volume of the organic reagent so that the reaction vessel was half-filled, and by ensuring that the stirring was efficient. As a further precaution the maximum reaction pressure was restricted to 500 atm.

A further risk arises in compressing the nitrous oxide which is liable to escape from the compressor (Fig. 1) past the mercury seal into the pressure-transmitting medium. When this is water no harm results, but if a hydrocarbon oil is used serious explosions may occur in the compression system, and indeed have done so.

This work is the subject of B.P. Applns. 24780/48, 822/49, and 19509/49.

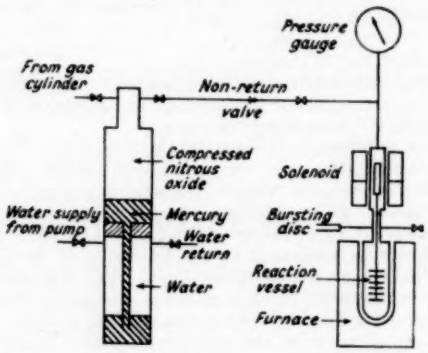
Experimental.

Microanalyses are by Dr. A. F. Colson. All m. p.s are corrected.

Apparatus and Procedure.—All reactions were carried out in a stainless-steel autoclave of 75-c.c. capacity and 3000 atm. maximum working pressure, fitted with a bursting disc (1000 atm.) close to the head of the vessel (Fig. 1). The vessel was heated by a copper-block electric furnace, and stirred by a magnetically operated reciprocating stirrer. The temperatures measured were the furnace temperatures adjacent to the outer surface of the vessel. The nitrous oxide was introduced into the reaction vessel by means of a compressor, consisting of two cylinders, one above the other, with a dip pipe from the upper cylinder reaching almost to the bottom of the lower. Initially the lower cylinder was full of mercury and the upper contained nitrous oxide. Water was then forced into the upper portion of the lower cylinder by means of a piston-type pump. Mercury was thus transferred to the upper cylinder and the gas was compressed and passed through the outlet valve into the reaction vessel.

The vessel was charged with 30—40 c.c. of the organic liquid, closed after the air had been displaced by nitrous oxide at atmospheric pressure, and heated to the required temperature. The stirrer was then started and nitrous oxide admitted until the required pressure was attained. When the reaction was completed, the vessel was cooled to room temperature and the pressure released. The gases were usually passed through a trap cooled in liquid air. The trap was then allowed to warm slowly to room temperature and the residual contents were combined with the contents of the reaction vessel.

Fig. 1.



Nitrous Oxide.—The nitrous oxide used was found to have the following percentage composition: N_2O, 99·8; non-condensables, 0·2%; higher oxides of nitrogen, trace. After 18 hours at 300°/1000 atm. the non-condensables had increased to 1·5%.

Infra-red Spectrography.—A Grubb-Parsons model S3 spectrometer, equipped with a rock-salt prism, thermal detector, A.C. amplifier, and pen recorder, was used for the infra-red examinations.

Reaction of Nitrous Oxide with Olefins.—Ethylene. The autoclave was charged with *cyclo*hexane (20 c.c.), closed, and heated to 300°. Ethylene was admitted to a pressure of 230 atm., followed by nitrous oxide until the pressure rose to 500 atm., and the contents were then stirred under these conditions for 4 hours. After the vessel had been cooled the pressure was released slowly and the gases were passed through a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid (500 c.c.). The precipitate (1·1 g.) was collected, washed, and crystallised from ethanol, and was identified as acetaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 167°.

The liquid product was distilled. The first fraction (1·7 c.c.), b. p. 20—30°, consisted largely of acetaldehyde. The remainder, b. p. mainly about 80°, was chiefly *cyclo*hexane, and there remained a high-boiling residue (3·1 g.). The *cyclo*hexane fraction, on treatment with a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid, gave a small amount of crotonaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 187—188°.

Propylene. The reaction vessel was cooled to −180° and evacuated, and propylene (30 c.c.) was allowed to distil into it. The temperature was then raised to 300°, nitrous oxide was admitted to a pressure of 500 atm., and the mixture was stirred under these conditions for 2 hours. The vessel was cooled to −180° and the pressure slowly released. The contents of the vessel were allowed to warm to −60°, kept at this temperature until no more gas was evolved, and then distilled. A fraction, b. p. 0—5°, was collected as a gas (350 c.c. at N.T.P.) and analysed by infra-red spectrography. It was proved to consist mainly of methyl*cyclo*propane by the similarity of its spectrum with that published by Condon and Smith (*J. Amer. Chem. Soc.*, 1947, **69**, 965). The presence of approximately 16% of acetaldehyde, 10% of propylene, and 1·5% of nitrous oxide was also established.

A small fraction, b. p. 5—23°, was treated with 2 : 4-dinitrophenylhydrazine and yielded acetaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 167°.

The main fraction (6·3 c.c.) b. p. 45—56°, reacted with benzaldehyde to give dibenzylideneacetone, m. p. and mixed m. p. 110·5—111·5°, and with dimedone to give propaldehyde dimethone, m. p. and mixed m. p. 155°.

The approximate proportions of acetone and propaldehyde in the mixture were determined by infra-red spectrography. Known mixtures of acetone and propaldehyde were examined in the form of 10% solutions in *n*-hexane; the optical densities for the 8·3-μ band in a 0·09-mm. cell were measured by a base-line density method and plotted against the concentration. By using the curve so obtained the acetone content of the unknown mixture was determined. Propaldehyde was determined by measurement of the optical density of the 5·82-μ band and calculation of the carbonyl content from the known molar extinction coefficient; part of the absorption at 5·82 μ was of course due to acetone, but an appropriate correction was applied by use of the known molar extinction coefficient for acetone at 5·82 μ and the figure for the acetone content derived from measurement of the 8·3-μ band. These determinations showed that the mixture contained 66% of acetone and 32% of propaldehyde.

The material of b. p. >56° (4·8 c.c.) appeared to be a complex mixture of unsaturated carbonyl compounds and a little undistillable resin.

Hept-1-ene. The olefin (28 c.c.) was treated with nitrous oxide at 350°/200 atm. for 1 hour. Distillation of the product (25 c.c.) gave fractions: (i) b. p. 78—86°, 7·8 c.c.; (ii) b. p. 86—123°, 1·3 c.c.; (iii) b. p. 123—127°, 1·0 c.c.; (iv) b. p. 127—146°, 0·7 c.c.; (v) b. p. 146—155°, 4·7 c.c.; and (vi) residue, 9·5 c.c. Fraction (i) was mainly unchanged olefin. From fraction (iii) were prepared hexanal semicarbazone, m. p. 105·5° (Found: C, 53·5; H, 9·4. Calc. for $C_7H_{15}ON_3$: C, 53·5; H, 9·6%), and 2 : 4-dinitrophenylhydrazone, m. p. 107°.

Fraction (v) reacted with dimedone to give heptanal dimethone, m. p. and mixed m. p. 99·5°, and with semicarbazide to give heptan-2-one semicarbazone, m. p. and mixed m. p. 121°. The residue (vi) was a complex mixture of condensation products which was not further investigated.

Inspection of the distillation curve and comparison of the infra-red absorption spectra of known mixtures with those of fractions (ii)—(v) indicated that the carbonyl compounds were present in the approximate proportions: hexanal (24%), heptanal (50%), and heptan-2-one (26%).

Pent-2-ene. The olefin (2 × 30 c.c.) was treated with nitrous oxide at 300°/500 atm. for 4 hours. After the vessel had been cooled the pressure was released slowly and the gases were passed through a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. The precipitate was collected and identified as acetaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 167°.

The liquid product was distilled and gave fractions: (i) b. p. 30—38°, 2 c.c.; (ii) b. p. 38—96°, 6 c.c.; (iii) b. p. 96—102°, 2·8 c.c.; and (iv) b. p. 102—103·5°, 31 c.c.; there remained a small high-boiling residue. Fractions (i) and (ii) were shown to contain aldehydes by Schiff's reaction, and fraction (ii) gave propaldehyde dimethone, m. p. and mixed m. p. 152—154°, and 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 149·5—151°. Fraction (iv) was a mixture of pentan-2-one and pentan-3-one; it reacted with benzaldehyde to give propyl styryl ketone dimer, m. p. and mixed m. p. 196—197·5°. Comparison of the infra-red absorption spectrum of fraction (iv) with those of mixtures of known composition showed that it contained pentan-2-one (*ca.* 56%) and pentan-3-one (*ca.* 44%).

cyclo*Hexene.* The olefin (40 c.c.) was treated with nitrous oxide at 300°/500 atm. for 2 hours, and the product was distilled, yielding fractions: (i) b. p. <90°, 3·5 c.c.; (ii) b. p. 90—153°, 2·6 c.c.; (iii) b. p. 153—156°, n_D^{20} 1·4505, 23·5 c.c.; and (iv) high-boiling residue, 11·5 c.c. Fraction (i) consisted of unchanged *cyclo*hexene and a little water; fraction (iii) was *cyclo*hexanone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 161·5°; semicarbazone, m. p. and mixed m. p. 168·5°); and fraction (iv) appeared to be a complex mixture of condensation product of *cyclo*hexanone.

The infra-red absorption spectra of the fractions showed no bands attributable to *cyclo*hexene oxide.

Stilbene. The olefin (40 g.) was treated with nitrous oxide at 300°/500 atm. for 4 hours. The product was dissolved in ether and washed with 10% potassium carbonate solution and then with water. The washings were acidified with hydrochloric acid, and the precipitate was collected (5·2 g.) and identified as benzoic acid, m. p. and mixed m. p. 122°. The ethereal solution was then washed repeatedly with a 5% sodium hydrogen sulphite solution; the washings were saturated with potassium carbonate and extracted with ether, and the extract was dried ($MgSO_4$). After removal of the ether by distillation there remained benzaldehyde (4·3 g.) (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 238°; semicarbazone, m. p. and mixed m. p. 234—235°).

The original ethereal solution, after the treatment described above, was freed from ether by distillation and distilled with steam; the distillate was extracted with ether, and the extract was dried ($MgSO_4$) and evaporated. The residue, a low-melting solid, was crystallised from methanol, giving stilbene (7·2 g.), m. p. and mixed m. p. 122—123°. The mother-liquors were evaporated and the residue crystallised from light petroleum (b. p. 60—80°) giving deoxybenzoin (3·2 g.), m. p. and mixed m. p. 55—56° (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 201—203°).

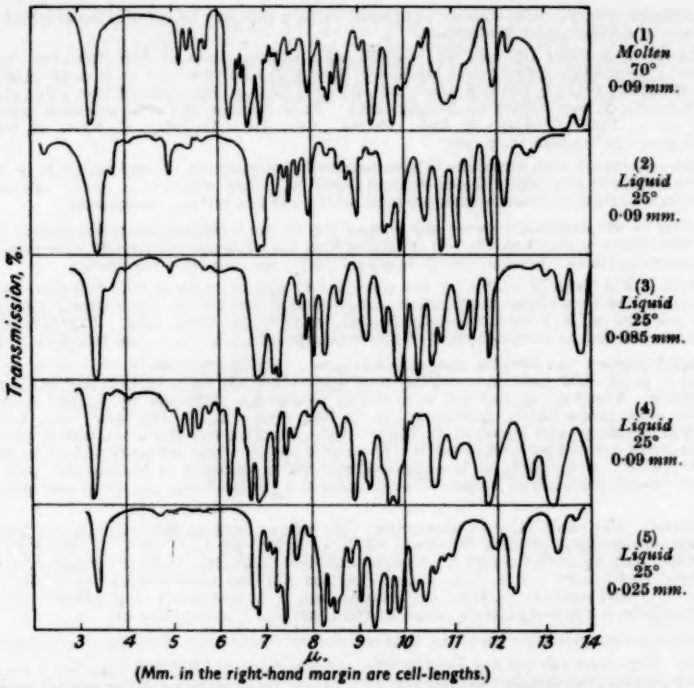
The steam-distillation residue was extracted with ether, and the extract was dried ($MgSO_4$) and evaporated. The residue (21 g.) was distilled *in vacuo* and gave two fractions. Fraction (i) (4·5 g.), b. p. mainly 140—150°/2 mm., solidified on cooling; crystallisation from light petroleum (b. p. 100—120°) gave deoxybenzoin, m. p. and mixed m. p. 55—56°. Fraction (ii) (13·1 g.), b. p. mainly 185—190°/2 mm., was a viscous oil which solidified after several hours; crystallisation from ethanol gave needles of 1 : 2 : 3-*triphenylcyclopropane*, m. p. 63° (Found: C, 93·15; H, 6·5%; *M*, 270. $C_{21}H_{18}$ requires C, 93·35; H, 6·65%; *M*, 270). Its infra-red absorption spectrum (Fig. 2) showed bands at 6·25 and 6·68 μ, attributable to phenyl groups. The absorption at 9·75 μ—which was shown by the

compound when examined as a solid film, in the liquid state, and in solution in hexane—was ascribed to the *cyclo*propane ring, although the diagnostic band usually lies in the range 9·8—10 μ.

Acenaphthylene. A solution of acenaphthylene (5 g.) in *cyclo*hexane (30 c.c.) was treated with nitrous oxide at 300°/500 atm. for 4 hours. The resulting solution was evaporated and the residue distilled with steam. Crystals (2 g.) which formed in the distillate were collected and identified as acenaphthenone, m. p. and mixed m. p. 119°.

iso*Butene*. The reaction vessel was cooled to −180° and evacuated, and *iso*butene (35 c.c.) was distilled into it and treated with nitrous oxide at 250°/500 atm. for 2 hours. After the vessel had been cooled the pressure was released and the exit gases were passed through a series of traps immersed in liquid air. The non-condensable gas contained nitrogen (97·8%), oxygen (1·83%), and traces of carbon monoxide and hydrocarbons.

FIG. 2.


Transmission, %.
(1) Molten 70° 0·09 mm.
(2) Liquid 25° 0·09 mm.
(3) Liquid 25° 0·085 mm.
(4) Liquid 25° 0·09 mm.
(5) Liquid 25° 0·025 mm.
3 4 5 6 7 8 9 10 11 12 13 14
μ.

(Mm. in the right-hand margin are cell-lengths.)

(1) 1 : 2 : 3-*Triphenyl*cyclo*propane*.
(2) spiro[2 : 5]*Octane*.
(3) 1-*Methyl*-1-neo*pentyl*cyclo*propane*.
(4) 1-*Methyl*-1-*phenyl*cyclo*propane*.
(5) iso*Butyl* cyclo*propyl ether*.

The products from six experiments were combined for working up. The contents of the liquid-air traps were kept at −50° to −60° until no more nitrous oxide was evolved. The residue was then distilled through a train of wash-bottles containing sodium hydrogen sulphite solution followed by sodium carbonate solution, through calcium chloride drying tubes, and finally condensed in a receiver cooled to −20°. The condensate was fractionally distilled and gave *iso*butene (38 c.c.), b. p. −8°, and a fraction (11·6 c.c.), b. p. 6—22°; most of the latter distilled at 19—22° and had m. p. −100°, n_D^9 1·3785 (Found: C, 85·5; H, 14·2%; *M*, 71·6. Calc. for C_5H_{10}: C, 85·7; H, 14·3%; *M*, 70). Gustavson and Popper (*J. prakt. Chem.*, 1898, **58**, 458) give b. p. 21°, m. p. −108·4 to −107·3°, n_D^{17} 1·3659 for 1 : 1-dimethyl*cyclo*propane. The infra-red absorption spectrum of the sample was identical with that of 1 : 1-dimethyl*cyclo*propane (Derfer, Pickett, and Boord, *J. Amer. Chem. Soc.*, 1949, **71**, 2782).

The liquid products from the reaction were fractionally distilled; the main fraction, b. p. 54—58°, consisted of acetone (dibenzylidene derivative, m. p. and mixed m. p. 113·5°). A small fraction, b. p. 36—48°, contained propaldehyde (dimethone, m. p. and mixed m. p. 152°). A high-boiling residue contained unsaturated carbonyl compounds but no *iso*butaldehyde was detected. The infra-red absorption spectra of the fractions showed no bands atributable to *iso*butene oxide.

*Methylene*cyclo*hexane*. The olefin (40 c.c.) was treated with nitrous oxide at 300°/400 atm. for 4 hours. The combined products from three runs (98 c.c.) were distilled and the fraction, b. p.

75°/760 mm.—140°/25 mm., (68 c.c.) was washed repeatedly with 5% sodium hydrogen sulphite solution, then with water and 10% sodium carbonate solution. The combined washings were treated with excess of sodium carbonate and distilled in steam. The organic portion of the distillate was separated, dried ($CaCl_2$), and distilled. It consisted almost entirely of *cyclo*hexanone, b. p. 156—157° (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 161°; semicarbazone, m. p. and mixed m. p. 165°).

The oil (32·5 c.c.) which had remained undissolved in the sodium hydrogen sulphite solution was dried ($CaCl_2$) and fractionally distilled; the main fraction, b. p. 125—127·5°, n_D^{20} 1·4469, was *spiro*[2 : 5]octane (Found : C, 87·3; H, 12·6%; *M*, 109. Calc. for C_8H_{14} : C, 87·3; H, 12·7%; *M*, 110). Its infra-red absorption spectrum (Fig. 2) was identical with that of an authentic specimen, b. p. 125·7°, n_D^{20} 1·4468, prepared by the method used by Shortridge *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 949).

The infra-red spectrum of the original mixture, b. p. 75°/760 mm.—140°/25 mm., showed that it contained 45 ± 5% of *spiro*[2 : 5]octane, estimated from the optical density of the 11·87-μ band, and 48 ± 5% of *cyclo*hexanone, estimated from the 11·56-μ band.

2 : 4 : 4-*Trimethylpent*-1-*ene*. The olefin (2 × 50 c.c.) was treated with nitrous oxide at 300°/500 atm. for 2 hours, and the product (85 c.c.) was distilled. This gave fractions : (i) b. p. <105°, 20 c.c.; (ii) b. p. 105—119°, 5 c.c.; (iii) b. p. 119—120·5°, 13 c.c.; (iv) b. p. 120·5—124°, 12 c.c.; (v) b. p. 124—124·5°, 6·5 c.c.; (vi) b. p. 124·5—131°, 3·5 c.c.; and (vii) b. p. 131—144°, 6 c.c.

Fraction (i) was mainly unchanged olefin. Fraction (v) had n_D^{20} 1·4041 and was identified as 4 : 4-dimethylpentan-2-one (Found : C, 73·5; H, 12·6. Calc. for $C_7H_{14}O$: C, 73·7; H, 12·3%); it formed a semicarbazone, m. p. 176° (Found : C, 56·6; H, 9·6; N, 24·7. Calc. for $C_8H_{17}ON_3$: C, 56·15; H, 9·9; N, 24·45%), and a 2 : 4-dinitrophenylhydrazone, m. p. 102° [Whitmore *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 2035) give b. p. 124°, n_D^{20} 1·4030, for the ketone, m. p. 176° for the semicarbazone, and m. p. 100° for the ddinitrophenylhydrazone].

Fraction (vi) was also essentially 4 : 4-dimethylpentan-2-one, and fractions (iii) and (iv) contained this ketone mixed with a hydrocarbon. Fractions (iii) and (iv) were combined and added rapidly to a stirred solution of sodium hypochlorite which had been freshly prepared by chlorination of sodium hydroxide (43·6 g.) in water (310 c.c.). The temperature rose to 70° and was kept at 65—70° by occasional cooling until the reaction was complete. The excess of hypochlorite was then destroyed by addition of sodium hydrogen sulphite solution, and the mixture was made strongly alkaline with sodium hydroxide, and distilled with steam. The organic layer of the distillate was separated, dried (Na_2SO_4), and distilled. The main fraction, b. p. 128—128·5°, n_D^{20} 1·4179, was 1-*methyl*-1-neo*pentyl*-*cyclopropane* (Found : C, 85·5; H, 14·3%; *M*, 125. C_9H_{18} requires C, 85·7; H, 14·3%; *M*, 126). Its infra-red absorption spectrum (Fig. 2) showed a strong band at 9·86 μ, characteristic of the *cyclo*propane ring.

The steam-distillation residue was acidified with sulphuric acid and distilled in steam. The distillate (140 c.c.) was extracted several times with ether, and the extract dried (Na_2SO_4) and fractionally distilled. This gave $\beta\beta$-dimethylbutyric acid (6·7 g.), b. p. 176—180°, n_D^{20} 1·4110, which was characterised as the anilide, m. p. 132°. Homeyer, Whitmore, and Wallingford (*J. Amer. Chem. Soc.*, 1933, **55**, 4211) give b. p. 183°, n_D^{20} 1·4096, for the acid and m. p. 131° for the anilide.

The infra-red absorption spectra of fractions (ii)—(vi) showed that 4 : 4-dimethylpentan-2-one, estimated from the optical density of the 5·81-μ band, and 1-methyl-1-*neo*pentyl*cyclo*propane, estimated from the 9·86-μ band, were present in the mixture in approximately equimolecular proportion.

2-*Phenylpropene*. The olefin (40 c.c.) was treated with nitrous oxide at 280°/500 atm. for 4 hours, and the combined products from four runs (151 c.c.) were distilled under reduced pressure. This gave two main fractions : (i) b. p. 69—69·5°/20 mm., n_D^{20} 1·5156, 27·5 c.c.; and (ii) b. p. 91·5—92°/20 mm., 52 c.c.; a very high-boiling residue (36 c.c.) remained.

Fraction (i) was 1-methyl-1-phenyl*cyclo*propane (Found : C, 90·8; H, 9·2. Calc. for $C_{10}H_{12}$: C, 90·9; H, 9·1%). Whitmore, Weisgerber, and Shabica (*J. Amer. Chem. Soc.*, 1943, **65**, 1469) give b. p. 91°/50 mm., n_D^{20} 1·5160, for this hydrocarbon. Its infra-red absorption spectrum (Fig. 2) showed a band at 9·83 μ. An absorption band between 9·8 and 10 μ. is normally exhibited by *cyclo*propane derivatives.

Fraction (ii) was acetophenone (semicarbazone, m. p. and mixed m. p. 201—202°; 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 248°).

1 : 1-*Diphenylethylene*. The olefin (40 c.c.) was treated with nitrous oxide at 300°/500 atm. for 4 hours. The products from two experiments (70 g.) were combined and distilled in steam. The distillation residue was extracted with benzene, the benzene removed by distillation, and the residue distilled under reduced pressure. Most of it distilled at 128—175°/2 mm. leaving a tarry residue. The distillate was set aside at 0° for 24 hours, and the crystals which formed were then collected and washed with pentane at −20°. They were identified as benzophenone, m. p. and mixed m. p. 41—42·5° (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 233—234°).

The mother liquor and washings from the crystallisation were combined with the organic layer of the steam-distillate and added to a mixture of ethanol (36 c.c.), water (7 c.c.), and hydroxylamine hydrochloride (11 g.). Sodium hydroxide (20 g.) was added gradually, and the mixture was then boiled under reflux for 5 minutes, cooled, and diluted with water (200 c.c.). The oil (10·6 g.) was separated, washed with dilute aqueous sodium hydroxide, dried ($CaCl_2$), and distilled under reduced pressure. It was obviously a mixture and boiled mainly at 132—145°/12 mm. Its infra-red absorption spectrum indicated that it was free from benzophenone and showed a prominent band at 9·87 μ. attributable to the *cyclo*propane ring. By applying to measurements of this band a molar extinction coefficient of 50, derived from a study of the spectra of known *cyclo*propanes, it was estimated that the mixture contained approximately 20% of 1 : 1-diphenyl*cyclo*propane.

Acidification of the aqueous alkaline solution from the hydroxylamine reaction gave benzophenone oxime, m. p. 142°.

1 : 1-*Bis*-p-*methoxyphenylethylene*. The olefin (44 g.) was treated with nitrous oxide at 280°/500 atm. for 4 hours, and the product (45 g.) was dissolved in light petroleum (400 c.c.; b. p. 60—80°), and the solution boiled with charcoal and filtered. On cooling, the solution deposited crystals (8·3 g.) of *pp'*-dimethoxybenzophenone, m. p. 143·5° (Found: C, 74·5; H, 5·6. Calc. for $C_{15}H_{14}O_3$: C, 74·4; H, 5·8%). It formed a 2 : 4-dinitrophenylhydrazone, m. p. 199·5° (Found: N, 12·5. Calc. for $C_{21}H_{18}O_6N_4$: N, 13·2%).

The light petroleum solution was evaporated and the residue dissolved in ethanol (50 c.c.); water (7·5 c.c.), hydroxylamine hydrochloride (7·5 g.), and potassium hydroxide (8 g.) were added, and the mixture was boiled under reflux for 15 minutes, cooled, diluted with water (200 c.c.), and extracted with benzene. The benzene was removed by distillation and the residue distilled in a vacuum (0·002 mm.). The pale yellow, semi-solid distillate (2 g.) was crystallised from ethanol giving 1 : 1-*bis*-p-*methoxyphenylcyclopropane* as needles, m. p. 59·5—60·5° (Found: C, 80·0; H, 7·2. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%).

*Methylene*cyclo*butane*. A solution of the olefin (13 c.c.) in decalin (27 c.c.) was treated with nitrous oxide at 300°/450 atm. for 4 hours, and the product was fractionally distilled. There was obtained a small fraction, b. p. 118—135°, which reacted with 2 : 4-dinitrophenylhydrazine to give *cyclo*pentanone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 141—142°.

iso*Butyl vinyl ether*. The olefin was treated with nitrous oxide at 280°/500 atm. for 4 hours, and the product from a series of runs (157 c.c.) was distilled. This gave fractions: (i) b. p. 60—97°, 4 c.c.; (ii) b. p. 97—97·5°, n_D^{20} 1·3865, 45 c.c.; (iii) b. p. 97·5—110°, 6 c.c.; (iv) b. p. 110—113°, n_D^{20} 1·4000, 34 c.c.; and (v) b. p. 113—150°, 11 c.c.; there remained an undistillable residue, probably a polymer of *iso*butyl vinyl ether.

Fraction (ii) was *iso*butyl formate; on hydrolysis with potassium hydroxide solution it gave potassium formate and *iso*butyl alcohol, which was characterised as the α-naphthylcarbamate, m. p. 99—100°.

Fraction (iv) had a saponification value of 62 and therefore probably contained about 10% of *iso*butyl formate. Fractions (iii)—(v) were therefore combined, added to a solution of potassium hydroxide (50 g.) in methanol (200 c.c.), and boiled under reflux for 2·5 hours. The solution was cooled and diluted with water, and the oil was separated, washed with water, dried ($CaCl_2$), and fractionally distilled. The main fraction (20 c.c.), b. p. 112—115°, was boiled under reflux with sodium (2·7 g.) for 2 hours and redistilled. This gave iso*butyl* cyclo*propyl ether* (15 c.c.), b. p. 114·5°, n_D^{20} 1·4032 (Found: C, 74·5; H, 12·6%; *M*, 113. $C_7H_{14}O$ requires C, 73·7; H, 12·3%; *M*, 114). Its infra-red absorption spectrum (Fig. 2) showed a prominent band at 9·88 μ characteristic of the *cyclo*propane ring.

2 : 3-*Dihydropyran*. The olefin (50 c.c.) was treated with nitrous oxide at 300°/500 atm. for 2 hours, and the product (44·8 g.) was freed from unchanged dihydropyran by distillation at atmospheric pressure. The residue was distilled in a vacuum and gave a fraction (3·6 g.), b. p. 112—118°/19 mm., b. p. 212—214°/760 mm., which appeared to be δ-valerolactone (Found: sap. value, 555. Calc. for valerolactone: sap. value, 560). Oxidation with sodium dichromate and sulphuric acid gave glutaric acid, m. p. 94° (Found: equiv., 65·5. Calc. for glutaric acid: equiv., 66). The acid was characterised by conversion into the phenacyl ester, m. p. 104—105°.

Reaction of Nitrous Oxide with Miscellaneous Organic Compounds.—Benzhydrol. The carbinol (35 g.) was treated with nitrous oxide at 300°/400—500 atm. for 4 hours. The product was distilled in a vacuum and had b. p. mainly 133—138°/1·5 mm. The distillate partly crystallised on storage, and the crystals were collected and washed with pentane. This gave unchanged benzhydrol, m. p. and mixed m. p. 63—65°. Treatment of the filtrate with 2 : 4-dinitrophenylhydrazine gave a small amount of benzophenone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 239—241°.

Benzoin. Benzoin (18 g.) was treated with nitrous oxide at 300°/500 atm. for 4 hours. The product was distilled in a vacuum and gave benzil (3·5 g.), b. p. 160—164°/2 mm., m. p. and mixed m. p. 94—96° (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 239—241°).

Benzaldehyde. The aldehyde (40 c.c.), carefully purified by washing it with sodium carbonate solution, drying it, and distilling it in a vacuum, was treated with nitrous oxide at 300°/500 atm. for 4 hours. After the reaction vessel had been cooled, the product (39·7 g.) was immediately dissolved in chloroform (250 c.c.) and extracted with 10% sodium carbonate solution. Acidification of the alkaline extract yielded benzoic acid (34·9 g.), m. p. and mixed m. p. 120—121°.

The authors are indebted to Mr. F. Bebbington and Mrs. H. Malkin for assistance in carrying out the experimental work described above.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, RESEARCH DEPARTMENT,
ALKALI DIVISION, NORTHWICH, CHESHIRE. [*Received, January 24th* 1951.]

667. *Oxidation of Organic Compounds by Nitrous Oxide. Part II.* Tri- and Tetra-substituted Ethylenes.*

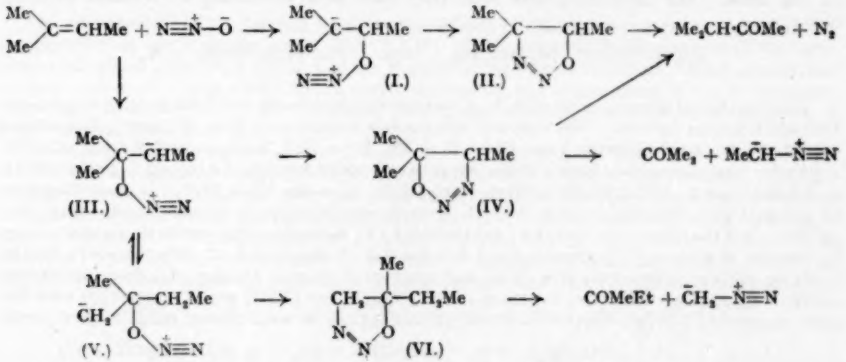
By F. S. Bridson-Jones and G. D. Buckley.

The reaction of nitrous oxide with nine trisubstituted and two tetra-substituted ethylenes has been studied at 250—300°/100—500 atm. Tri- and tetra-phenylethylenes failed to react, but the remaining examples readily gave carbonyl compounds. The fundamental reactions were the same as with simpler olefins (cf. Part I), but the additional substituents increased the number of possible reactions and resulted in the formation of more complex mixtures of products.

The results were consistent with the reaction mechanism advanced in Part I.

Tri- and tetra-substituted ethylenes, with two exceptions, reacted readily with nitrous oxide at 250—300°/100—500 atm., in many cases with the formation of complex mixtures. It is evident that an olefinic hydrocarbon CHX=CYZ may react with nitrous oxide to form two isomeric 1 : 2 : 3-oxadiazolines, and when X, Y, and Z are all different the *A*-type decomposition (cf. Part I) of the two isomers may lead to three isomeric ketones. Even in the simplest case (X = Y = Z) the simultaneous occurrence of *A*- and *B*-type decompositions may lead to a mixture of several products.

Two examples of the simple cases were studied. Triphenylethylene failed to react with nitrous oxide, but 2-methylbut-2-ene reacted readily. The main product was the expected 3-methylbutan-2-one, which is the only ketone which can be formed by the *A*-type decomposition of either 4 : 5 : 5-(IV) or 4 : 4 : 5-trimethyl-1 : 2 : 3-oxadiazoline (II); small amounts of acetaldehyde, acetone, butan-2-one, ethylene, 1 : 1 : 2-trimethyl*cyclo*propane, and a hydrocarbon, C_7H_{14}, which was probably the unknown 1 : 1 : 2 : 3-tetramethyl*cyclo*propane, were however also formed.



B-Type decomposition of (IV) would lead to the production of acetone and diazoethane. The production of diazoethane may be inferred from the appearance of ethylene, arising by thermal decomposition, and of acetaldehyde and 1 : 1 : 2 : 3-tetramethyl*cyclo*propane, arising from the reaction of diazoethane with nitrous oxide and 2-methylbut-2-ene, respectively.

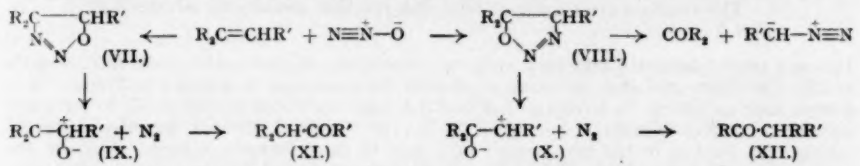
It is also possible, though less probable, that some of the acetone and acetaldehyde arose from *B*-type decomposition of (II).

All the products, except butan-2-one and 1 : 1 : 2-trimethyl*cyclo*propane, may therefore be accounted for as decomposition products of the two oxadiazolines (II and IV) which would be formed by direct addition of nitrous oxide to the double bond. The presence of butan-2-one and trimethyl*cyclo*propane appears to be explicable only by postulation of the formation of a small amount of 5-ethyl-5-methyl-1 : 2 : 3-oxadiazoline (VI), which like all other 5 : 5-disub-

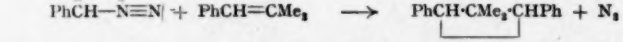
* Part I, preceding paper.

stituted 1 : 2 : 3-oxadiazolines (cf. Part I) would undergo only *B*-type decomposition to give butan-2-one and diazomethane; the diazomethane would then react with 2-methylbut-2-ene to give 1 : 1 : 2-trimethyl*cyclo*propane. (VI) might have been formed by the reaction of nitrous oxide with 2-methylbut-1-ene, but care was taken to ensure that the 2-methylbut-2-ene was free from isomers, and no isomerisation occurs when the olefin is heated alone at 300°. It must therefore be assumed that rearrangement occurs when the olefin is attacked by nitrous oxide. Attack may occur either at the 2- or the 3-position to give (III) and (I), respectively. (I), if it is formed, evidently cyclises to (II), and (III) must largely cyclise normally to (IV). But in order to account for the formation of (VI) it must be assumed that part of (III) isomerises to (V) by migration of a proton from the 1-position to the 3-position, and that (V) then undergoes a normal cyclisation to (VI).

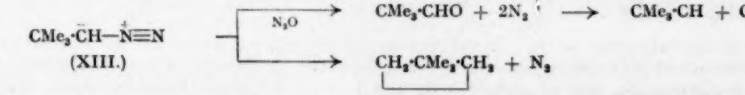
Three examples of the case Y = Z ≠ X, which can yield two isomeric ketones by *A*-type decomposition of the two isomeric oxadiazolines, were studied.



2-Methyl-1-phenylprop-1-ene reacted with nitrous oxide to give 3-phenylbutan-2-one (XII; R = Me, R′ = Ph) and small amounts of *iso*butyrophenone (XI; R = Me, R′ = Ph), acetone, propaldehyde, and 1 : 1-dimethyl-2 : 3-diphenyl*cyclo*propane. It may therefore be inferred that nitrous oxide reacted with the olefin to give mainly 5 : 5-dimethyl-4-phenyl-1 : 2 : 3-oxadiazoline (VIII; R = Me, R′ = Ph), together with a small amount of 4 : 4-dimethyl-5-phenyl-1 : 2 : 3-oxadiazoline (VII; R = Me, R′ = Ph). (VII) evidently underwent only *A*-type decomposition to *iso*butyrophenone, whereas (VIII) underwent both types of decomposition to give 3-phenylbutan-2-one on the one hand and acetone and ω-diazotoluene on the other. The diazo-compound must then have been eliminated by reaction with the olefin:



The reaction of nitrous oxide with 2 : 4 : 4-trimethylpent-2-ene and with 4-propylhept-3-ene followed a similar pattern. The carbonyl compounds formed from 2 : 4 : 4-trimethylpent-2-ene were 2 : 2 : 4-trimethylpentan-3-one (XI; R = Me, R′ = Bu^t), acetone, and a trace of propaldehyde; there was also evidence of the presence of a minor amount of a second C_8 ketone which may have been 3 : 4 : 4-trimethylpentan-2-one (XII; R = Me, R′ = Bu^t). It must therefore be assumed that this olefin yields the two isomeric oxadiazolines in approximately equal proportions, and that the 5-*tert.*-butyl-4 : 4-dimethyl-1 : 2 : 3-oxadiazoline breaks down exclusively by reaction *A* to give (XI) whereas the 4-*tert.*-butyl-5 : 5-dimethyl-1 : 2 : 3-oxadiazoline breaks down by both reaction *A* to give (XII) and reaction *B* to give acetone and diaz*oneo*pentane (XIII). By analogy with other examples it was thought that (XIII) would react either with the olefin to give 2 : 3-di-*tert.*-butyl-1 : 1-dimethyl*cyclo*propane or with nitrous oxide to give pival-



aldehyde, but a careful examination of the reaction products showed that neither of these compounds was present. However, Conant, Webb, and Mendum (*J. Amer. Chem. Soc.*, 1929, **51**, 1246) have shown that pivalaldehyde slowly decomposes to carbon monoxide and *iso*butane even at 20°, and both these compounds and also 1 : 1-dimethyl*cyclo*propane were identified among the gaseous products of the nitrous oxide reaction. It must therefore be concluded that the diaz*oneo*pentane is eliminated partly by thermal decomposition to nitrogen and 1 : 1-dimethyl*cyclo*propane and partly by reaction with nitrous oxide to give pivalaldehyde which then decomposes at the high temperature.

4-Propylhept-3-ene reacted with nitrous oxide to give propaldehyde, heptan-4-one, and a

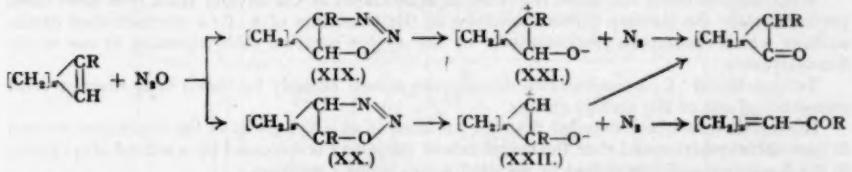
mixture of ketones, $C_{10}H_{20}O$. Degradation of the C_{10} ketones by the Schmidt reaction gave a mixture of amides, $C_{10}H_{21}ON$, which on hydrolysis gave a complex mixture of amines and carboxylic acids. Propylamine, 3-aminohexane, 4-aminoheptane, and butyric acid were identified, and the presence of a higher carboxylic acid was also established. The amide mixture must therefore have contained 3-butyramidohexane (XV), 4-propionamidoheptane (XVI) and 1-α-ethylvaleramidopropane (XIV). The ketones must therefore have been a mixture of 5-ethyloctan-4-one (XVII) and 4-propylheptan-3-one (XVIII).

$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CHEt{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$ (XVII.) $\xrightarrow{N_3H}$ $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CHEt{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$ (XIV.) + $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CHEt{\cdot}NH{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$ (XV.)

$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CHPr{\cdot}CO{\cdot}CH_2{\cdot}CH_3$ (XVIII.) $\xrightarrow{N_3H}$ $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CHPr{\cdot}NH{\cdot}CO{\cdot}CH_2{\cdot}CH_3$ (XVI.)

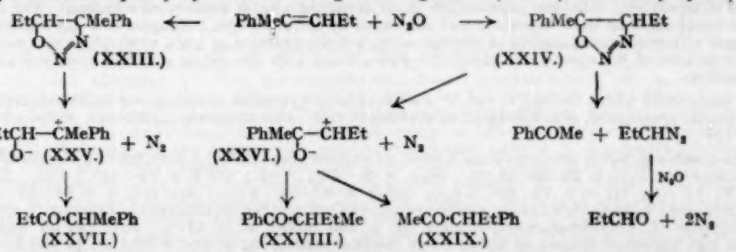
The three examples studied of the case $X=Y\neq Z$ were all 1-substituted *cyclo*alkenes. 1-Methyl*cyclo*hexene gave approximately equal amounts of 2-methyl*cyclo*hexanone and methyl *cyclo*pentyl ketone, and no other products were detected. 1-Phenyl*cyclo*hexene similarly gave 2-phenyl*cyclo*hexanone and *cyclo*pentyl phenyl ketone, but 1-methyl*cyclo*pentene gave only 2-methyl*cyclo*pentanone.

It is probable that the two isomeric 1 : 2 : 3-oxadiazolines (XIX and XX) were formed in each case, and evidently only *A*-type decomposition occurred.



The intermediate (XXI), arising from the breakdown of (XIX), rearranges to a stable form by migration of the hydrogen anion, but (XXII), arising from the breakdown of (XX), may become stabilised either by migration of the R anion or by ring-contraction. Ring-contraction evidently occurs to a large extent in the *cyclo*hexene series, but cannot occur in the *cyclo*pentene series since it would involve the formation of a highly strained four-membered ring from a strain-free five-membered ring.

One example of the case $X\neq Y\neq Z$ was studied. 2-Phenylpent-2-ene reacted with nitrous oxide to give acetophenone, propaldehyde, and a small amount of one or more ketones, $C_{11}H_{14}O$. It must therefore be supposed that the main initial reaction was the formation of 4-ethyl-5-methyl-5-phenyl-1 : 2 : 3-oxadiazoline (XXIV), but it is possible that the isomeric 5-ethyl-4-methyl-4-phenyl-1 : 2 : 3-oxadiazoline (XXIII) was also formed to a minor extent. It is presumed that (XXIII) broke down by reaction *A* to give nitrogen and (XXV), and that (XXIV) broke down partly by reaction *A* to give nitrogen and (XXVI) but mainly by reaction



B to give acetophenone and 1-diazopropane which was then oxidised to propaldehyde. (XXV) would then rearrange to 2-phenylpentan-3-one (XXVII) by migration of the hydrogen anion, and (XXVI) would rearrange either to α-methylbutyrophenone (XXVIII) by migration of the methyl anion or to 3-phenylpentan-2-one (XXIX) by migration of the phenyl anion.

Tetrasubstituted ethylenes may give rise to mixtures which are simpler or more complex than those derived from trisubstituted ethylenes according as the substituents are all the same or are different. In the two examples studied the four substituents were identical. Tetraphenylethylene failed to react with nitrous oxide, but 2 : 3-dimethylbut-2-ene readily gave 3 : 3-dimethylbutan-2-one; in addition a trace of propaldehyde was found, but no acetone. Tetramethyl-1 : 2 : 3-oxadiazoline therefore decomposes almost exclusively by the *A*-type reaction.

$$CMe_2{=}CMe_2 + N_2O \longrightarrow CMe_2{\cdot}COMe + N_2$$

The results now described are entirely consistent with the theory of the reaction mechanism advanced in Part I and it becomes possible to formulate tentative generalisations which enable the course of the reaction to be predicted in certain cases.

Since no formaldehyde was detected amongst the products of the reaction of nitrous oxide with any olefin it is evident that substitution in position 5 of the oxadiazoline ring is a necessary, though not a sufficient, condition for the occurrence of *B*-type decomposition. Thus *iso*butyl vinyl ether yields exclusively *iso*butyl formate with no detectable amount of *iso*butyl acetate, but propylene yields a trace only of acetaldehyde, and hept-1-ene yields approximately equimolecular amounts of hexanal and heptan-2-one. On the other hand 5 : 5-disubstituted oxadiazolines decompose only by the *B*-type reaction. Furthermore, 5 : 5-disubstituted oxadiazolines only must be formed from 1 : 1-disubstituted ethylenes, since in no case have there been found reaction products which could arise only by decomposition of 4 : 4-disubstituted oxadiazolines.

With trisubstituted ethylenes the point of attachment of the oxygen atom is in most cases predominantly the tertiary carbon, resulting in the formation of 4 : 5 : 5-trisubstituted oxadiazolines which decompose predominantly by the *A*-type reaction with migration of one of the 5-substituents.

Tetramethyl-1 : 2 : 3-oxadiazoline decomposes almost entirely by the *A*-type reaction with migration of one of the methyl groups.

It may therefore be concluded that the presence of an alkyl group in the 5-position favours *B*-type decomposition and that the magnitude of this effect is increased by a second alkyl group in the 5-position and diminished by an alkyl group in the 4-position.

This work is the subject of B.P. Applns. 24780/48, 822/49, and 19509/49.

Experimental.

(Microanalyses are by Dr. A. F. Colson. All m. p.s are corrected.)

Reaction of Olefins with Nitrous Oxide.—The apparatus and procedure are described in Part I.

2-Methylbut-2-ene. The olefin was prepared by dehydration of *tert.*-amyl alcohol with 35% (*v*/*v*) sulphuric acid, and purified by fractional distillation through a 50-plate column packed with stainless-steel gauze rings. This gave pure 2-methylbut-2-ene, b. p. 38·2—38·5°, n_D^{20} 1·3872; the infra-red absorption spectrum of the vapour was identical with that given in the "Catalogue of Selected Infra-Red Absorption Spectrograms" (Amer. Petr. Inst. Research Project 44, Nat. Bur. Standards).

The olefin was treated with nitrous oxide at 300°/500 atm. for 4 hours. After the vessel had been cooled to 20° the pressure was released and the gases were passed through a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid, a calcium chloride drying tower, and finally a trap cooled in liquid air. The non-condensable gases consisted almost entirely of nitrogen. The contents of the liquid-air trap were vaporised and examined by infra-red spectrography in a gas cell at 34 cm. pressure. They consisted mainly of nitrous oxide, but the presence of 1·5% of ethylene was established by comparison of the optical density of the 10·5-μ band with the values given by mixtures of known composition.

A precipitate which formed in the 2 : 4-dinitrophenylhydrazine solution was collected, crystallised from glacial acetic acid, and identified as acetaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 167°.

The combined liquid products from a series of experiments (120 c.c.) were fractionally distilled, and gave fractions: (i) b. p. 20—30°, 1 c.c.; (ii) b. p. 30—45°, 21 c.c.; (iii) b. p. 45—54°, 7·5 c.c.; (iv) b. p. 54—79°, 5·5 c.c.; (v) b. p. 79—80°, 6 c.c.; (vi) b. p. 80—94°, 4 c.c.; and (vii) b. p. 94—95°, 45 c.c.; there remained a small high-boiling residue which was not further investigated. Fraction (i) contained acetaldehyde (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 167°). Fraction (v) was water-soluble and consisted mainly of butan-2-one (semicarbazone, m. p. and mixed m. p. 137·5—139·5°; 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 110—111°). Fraction (vii) had n_D^{20} 1·3915, and was identified as 3-methylbutan-2-one (*p*-nitrophenylhydrazone, m. p. 107°; 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 121—122°).

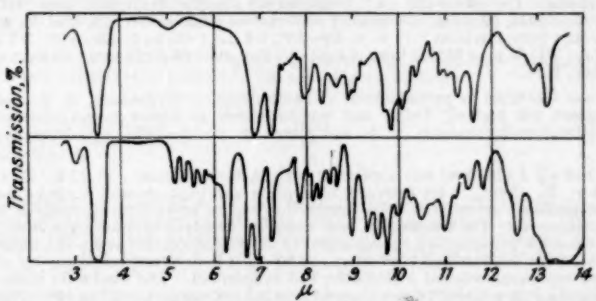
Fractions (ii)—(iv) were not completely water-soluble, but fraction (iii) was shown to contain acetone (dibenzylideneacetone, m. p. and mixed m. p. 109·5°; 2 : 4-dinitrophenylhydrazone, m. p. and mixed

m. p. 124°). The three fractions were combined and washed with water and then with sodium hydrogen sulphite until free from carbonyl compounds. The residual oil (12 c.c.) was dried ($CaCl_2$) and fractionally distilled to give fractions (*a*) b. p. 34—37°, 3·9 c.c.; (*b*) b. p. 37—50°, 3·1 c.c.; (*c*) b. p. 50—53°, 2·85 c.c.; (*d*) b. p. 53—76°, 1·35 c.c.; and (*e*) b. p. 76—81°, 0·65 c.c.

Fraction (*a*) had n_D^{20} 1·3832, and was essentially unchanged 2-methylbut-2-ene. Fraction (*c*) had n_D^{20} 1·3835 and consisted of 1 : 1 : 2-trimethyl*cyclo*propane (Found: C, 85·8; H, 14·1. Calc. for C_6H_{12}: C, 85·7; H, 14·3%) (Kishner, *J. Russ. Phys. Chem. Soc.*, 1912, **44**, 169, gives b. p. 52·8°, n_D^{20} 1·3866). The infra-red absorption spectrum of the vapour was identical with that of 1 : 1 : 2-trimethyl*cyclo*propane (Derfer, Pickett, and Boord, *J. Amer. Chem. Soc.*, 1949, **71**, 2482). Fraction (*e*) had n_D^{20} 1·3975 and was probably 1 : 1 : 2 : 3-*tetramethylcyclopropane* (Found: C, 85·3; H, 14·7. C_7H_{14} requires C, 85·7; H, 14·3%). Its infra-red absorption spectrum (see figure) did not agree with the spectrum of any known *cyclo*propane derivative, but the occurrence of prominent absorptions at 9·83 and 7·26 μ were consistent with the material being a *cyclo*propane derivative with a high methyl-group content.

2 : 4 : 4-*Trimethylpent-2-ene*. The olefin (40 c.c.) was treated with nitrous oxide at 300°/500 atm. for 4 hours. The vessel was then cooled, the pressure released, and the gaseous products passed through a series of traps cooled in liquid air. The non-condensable gases (4·89 l. at N.T.P.) were analysed in a constant volume gas analysis apparatus (Gooderham, *J. Soc. Chem. Ind.*, 1938, **57**, 388) and found to contain nitrogen (94·5%) and carbon monoxide (3·47%) together with traces of carbon dioxide, oxygen, and hydrogen.

The traps were then allowed to warm to −60° and kept at this temperature until no more gas was evolved; the gas consisted only of nitrous oxide and nitrogen. The residue in the traps was combined



(1) 1 : 1 : 2 : 3-*Tetramethylcyclopropane*. (2) 1 : 1-*Dimethyl*-2 : 3-*diphenylcyclopropane*.

with the contents of the reaction vessel and fractionally distilled to give fractions: (i) b. p. −10°—+21°; (ii) b. p. 21—47°, 0·2 c.c.; (iii) b. p. 47—50°, 1 c.c.; (iv) b. p. 50—57°, 3·5 c.c.; (v) b. p. 57—95°, 1·3 c.c.; (vi) b. p. 95—132°, 5·3 c.c.; (vii) b. p. 132—138°, 6·4 c.c.; and (viii) b. p. 138—158°, 4·9 c.c.; there remained a small high-boiling residue.

Fraction (i) was collected as a gas (420 c.c. at N.T.P.), and found by infra-red spectrography to contain approximately 40% by volume of nitrous oxide, 26% of 1 : 1-dimethyl*cyclo*propane, and 35% of *iso*butane.

Fraction (iii) contained propaldehyde (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 154—155°); fraction (iv) was mainly acetone (dibenzylidene derivative, m. p. and mixed m. p. 111—112°; 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 123—124°); and fraction (vi) was largely unchanged olefin.

Fraction (vii) had n_D^{20} 1·4081 and its infra-red absorption spectrum showed a prominent band at 5·81 μ, indicative of the carbonyl group (Found: C, 75·0; H, 12·6. Calc. for $C_8H_{16}O$: C, 75·0; H, 12·5%). It was identified as 2 : 2 : 4-trimethylpentan-3-one [semicarbazone, m. p. 135—136°; 2 : 4-dinitrophenylhydrazone, m. p. 159° (Found: C, 54·5; H, 6·0; N, 18·4. Calc. for $C_{14}H_{20}O_4N_4$: C, 54·55; H, 6·5; N, 18·2%) (Locquin and Leers, *Compt. rend.*, 1924, **179**, 55, give m. p. 132° for the semicarbazone; Byers and Hickinbottom, *J.*, 1948, 284, give m. p. 163—164° for the 2 : 4-dinitrophenylhydrazone)]. Reduction of the ketone with sodium and alcohol gave 2 : 2 : 4-trimethylpentan-3-ol, b. p. 145—148°, n_D^{20} 1·4289 (Found: C, 74·2; H, 14·0. Calc. for $C_8H_{18}O$: C, 73·85; H, 13·85%). This was characterised as the phenylurethane, m. p. 75·5—76·5° (Found: N, 5·7. Calc. for $C_{15}H_{23}O_2N$: N, 5·6%), and the 3 : 5-*dinitrobenzoate*, m. p. 101—102° (Found: N, 8·7. $C_{15}H_{20}O_6N_2$ requires N, 8·65%) (Whitmore and Houk, *J. Amer. Chem. Soc.*, 1932, **54**, 3714, give b. p. 148—150°, n_D^{20} 1·4288, for the alcohol; Haller and Bauer, *Compt. rend.*, 1910, **150**, 584, give m. p. 79° for the phenylurethane).

Fraction (viii) appeared to be a mixture of C_8 ketones (Found: C, 74·9; H, 12·4. $C_8H_{16}O$ requires C, 75·0; H, 12·5%). Attempts to prepare derivatives gave only oils or mixtures of indefinite melting point.

2-*Methyl*-1-*phenylprop*-1-*ene*. A solution of the olefin (19 c.c.) in *cyclo*hexane (20 c.c.) was treated with nitrous oxide at 300°/500 atm. for 4 hours. The product was distilled to give fractions: (i) b. p.

<52·5°, 1 c.c.; (ii) b. p. 52·5—53°, 1·4 c.c.; (iii) b. p. 53—79°, 2 c.c.; (iv) b. p. 79—83°, 18·6 c.c.; (v) b. p. <82°/3 mm., 1·3 c.c.; (vi) b. p. 82—87°/3 mm., 1·9 c.c.; (vii) b. p. 87—125°/3 mm., 0·7 c.c.; and (viii) b. p. 125—170°/3 mm., 4·2 c.c.; a small residue remained.

Fraction (i) contained propaldehyde (dimethone, m. p. and mixed m. p. 155°); fraction (ii) was essentially acetone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 123—124°); and fraction (iv) was unchanged *cyclo*hexane.

Fraction (vi) was a C_{10} ketone (Found: C, 80·7; H, 7·8. Calc. for $C_{10}H_{12}O$: C, 81·1; H, 8·1%). It was shown to be a methyl ketone by the iodoform reaction, and was characterised as the semicarbazone, m. p. 170—171° after repeated recrystallisation from ethanol (Found: N, 20·4. Calc. for $C_{11}H_{15}ON_3$: N, 20·5%). Darzens (*Compt. rend.*, 1905, **141**, 768) gives m. p. 172—173° for 3-phenylbutan-2-one semicarbazone. A portion of fraction (vi) was treated several times with alkaline sodium hypochlorite solution; most of the ketone reacted, but after separation of the oil and removal of the chloroform there remained a small amount of oil, which reacted with semicarbazide to give *iso*butyrophenone semicarbazone, m. p. 181—182° (depressed on admixture with the semicarbazone, m. p. 170—171°, above) (Found: N, 20·3. Calc. for $C_{11}H_{15}ON_3$: N, 20·5%).

The infra-red absorption spectrum of fraction (viii) showed that it contained carbonyl compounds. After removal of these by reaction with Girard's reagent P, the residual oil was redistilled to give 1 : 2-*dimethyl*-2 : 3-*diphenyl*cyclo*propane*, b. p. 102—112°/3·5 mm., n_D^{20} 1·5502 (Found: C, 92·3; H, 7·8. $C_{17}H_{18}$ requires C, 91·9; H, 8·1%). Its infra-red absorption spectrum (see figure) showed strong absorptions at 6·26, 7·26, and 9·74 μ which were consistent with the material's being a methylphenyl*cyclo*propane.

4-*Propylhept*-3-*ene*. The olefin (40 c.c.), prepared by Church, Whitmore, and McGrew's method (*J. Amer. Chem. Soc.*, 1934, **56**, 176), was treated with nitrous oxide at 300°/525 atm. for 4 hours. Distillation of the product gave fractions: (i) b. p. 50—53°, 0·3 c.c.; (ii) b. p. 53—145°, 3·7 c.c.; (iii) b. p. 145—145·5°, 5 c.c.; (iv) b. p. <95°/30 mm., 6 c.c.; (v) b. p. 95—96·5°/30 mm., 13·3 c.c.; and (vi) b. p. 96·5—160°/30 mm., 2 c.c.

Fraction (i) was identified as propaldehyde (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 150—151°); fraction (iii) had n_D^{20} 1·4090 and was identified as heptan-4-one (semicarbazone, m. p. 135·5°; 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 74—75°); and fraction (iv) contained unreacted olefin.

Fraction (v) had n_D^{20} 1·4243 and was a mixture of C_{10} ketones (Found: C, 77·3; H, 12·8. Calc. for $C_{10}H_{20}O$: C, 76·9; H, 12·8%). Its infra-red absorption spectrum showed a strong band at 5·81 μ, indicative of the carbonyl group, but all attempts to prepare crystalline derivatives with the usual reagents were unsuccessful. The ketone (7 g.) was therefore dissolved in chloroform (100 c.c.) and cooled to 0°; concentrated sulphuric acid (35 c.c.) was added to the stirred solution at 0—10°, followed by sodium azide (2·8 g.). After the mixture had been stirred at 20° for 1 hour it was poured on ice, and the chloroform solution was separated, washed with water, and evaporated. The semi-solid residue (4·7 g.) was hydrolysed by heating it in a sealed tube with concentrated hydrochloric acid at 190—200° for 12 hours. The mixture was diluted with water and extracted with ether; after the extract had been dried ($CaCl_2$) the ether was removed by distillation and the residue distilled under reduced pressure to give two main fractions. One of these, b. p. 55—69°/15 mm., formed *p*-bromophenacyl butyrate, m. p. and mixed m. p. 60—61° after repeated recrystallisation from ethanol. The second fraction, b. p. 109—115°/15 mm., was soluble in dilute aqueous sodium hydroxide, but attempts to prepare crystalline derivatives were unsuccessful (Found: equiv., 131. Calc. for $C_7H_{14}O_2$: equiv., 130).

The amines were isolated from the hydrochloric acid solution by treatment with sodium hydroxide and extraction with ether. The ethereal solution was dried (KOH) and fractionally distilled to give two basic fractions. One of these, which passed over with the ether, was treated with 2 : 4-dinitrophenylnitrourea; repeated recrystallisation of the product from ethanol gave *N*-2 : 4-dinitrophenyl-*N'*-propylurea as long yellow needles, m. p. 147° not depressed on admixture with an authentic specimen (Found: C, 44·9; H, 4·4; N, 20·8. Calc. for $C_{10}H_{12}O_5N_4$: C, 44·75; H, 4·45; N, 20·9%). The second fraction, b. p. 121—130°, reacted with phenyl *iso*cyanate to give a mixture of ureas; crystallisation of the mixture from methanol gave *N-phenyl*-N'-1-*propylbutylurea*, m. p. 137—138° not depressed on admixture with an authentic specimen (see below) (Found: C, 71·3; H, 9·1; N, 11·8. $C_{14}H_{22}ON_2$ requires C, 71·8; H, 9·4; N, 11·95%). The alcoholic mother liquors were evaporated to dryness and the residue crystallised from light petroleum (b. p. 60—80°) to give *N*-1-*ethylbutyl-N'-phenylurea*, m. p. 78° not depressed on admixture with an authentic specimen (see below) (Found: C, 70·8; H, 9·0; N, 12·3. $C_{13}H_{20}ON_2$ requires C, 70·9; H, 9·1; N, 12·75%). The base reacted with 2 : 4-dinitrophenylnitrourea to form a derivative which after repeated recrystallisation from ethanol gave N-2 : 4-*dinitrophenyl*-N'-1-*propylbutylurea*, m. p. 129—130° not depressed on admixture with an authentic specimen (see below).

An authentic specimen of 3-aminohexane, prepared by hydrogenation of hexan-3-one oxime, had b. p. 116—118°. With phenyl *iso*cyanate it gave *N*-1-ethylbutyl-*N'*-phenylurea (from light petroleum), m. p. 79° (Found: N, 12·8. Calc. for $C_{13}H_{20}ON_2$: N, 12·75%). It also reacted with 2 : 4-dinitrophenylnitrourea to give N-2 : 4-*dinitrophenyl*-N'-1-*ethylbutylurea*, small yellow needles (from a small volume of ethanol), m. p. 130·5—131° (Found: C, 50·2; H, 5·8; N, 17·7. $C_{13}H_{18}O_5N_4$ requires C, 50·3; H, 5·8; N, 18·05%).

An authentic specimen of 4-aminoheptane, prepared by hydrogenation of heptan-4-one oxime, had b. p. 134—136°. With phenyl *iso*cyanate it gave *N*-phenyl-*N'*-1-propylbutylurea, needles (from ethanol), m. p. 137—138° (Found: N, 11·8. Calc. for $C_{14}H_{22}ON_2$: N, 11·95%). Reaction with 2 : 4-dinitrophenylnitrourea gave *N*-2 : 4-dinitrophenyl-*N'*-1-propylbutylurea, yellow needles (from

ethanol), m. p. 130° (Found: C, 51·6; H, 5·9; N, 17·3. $C_{14}H_{20}O_5N_4$ requires C, 51·85; H, 6·15; N, 17·3%).

1-*Methyl*cyclo*pentene*. The olefin (35 c.c.) was treated with nitrous oxide at 300°/350—700 atm. for 3 hours. The product was distilled with steam, and the volatile oil was separated, dried ($CaCl_2$), and distilled to give fractions: (i) b. p. 72—90°, 3·2 c.c.; (ii) b. p. 90—133°, 2·6 c.c.; (iii) b. p. 133—138·5°, 1·4 c.c.; (iv) b. p. 138·5—139°, 6·1 c.c.; and (v) b. p. 139—152°, 1·6 c.c.

Fraction (i) was mainly unchanged olefin. Fraction (iv) had n_D^{20} 1·4320, and was identified as 2-methyl*cyclo*pentanone (Found: C, 72·8; H, 10·4. Calc. for $C_6H_{10}O$: C, 73·4; H, 10·2%) [2 : 4-*dinitrophenylhydrazone*, m. p. 155—157° (Found: C, 51·8; H, 5·3. $C_{12}H_{14}O_4N_4$ requires C, 51·8; H, 5·05%); semicarbazone, m. p. 180° (Found: N, 27·1. Calc. for $C_7H_{13}ON_3$: N, 27·1%)]. Van Rysselberge (*Bull. Acad. roy. Belg.*, 1926, **11**, 171) gives b. p. 139·5°, n_D^{20} 1·4347, for 2-methyl*cyclo*pentanone, and m. p. 184° for its semicarbazone.

Fractions (iii) and (v) also consisted largely of 2-methyl*cyclo*pentanone.

1-*Methyl*cyclo*hexene*. The olefin was treated with nitrous oxide at 300°/500 atm. for 5 hours, and the products from several experiments (243 g.) were combined and distilled to give fractions: (i) b. p. 105—115°, 81 c.c.; (ii) b. p. 115—157·5°, 11 c.c.; (iii) b. p. 157·5°, 17·5 c.c.; (iv) b. p. 157·5—162°, 29 c.c.; (v) b. p. 162—162·5°, 12·5 c.c.; (vi) b. p. 162·5—165°, 12·5 c.c.; (vii) b. p. 165°, 36 c.c.; and (viii) b. p. 165—210°, 19 c.c.

Fraction (i) was mainly unchanged olefin. Fractions (iii)—(vi) were shown to contain a methyl ketone by the iodoform reaction, and fraction (iii) reacted with semicarbazide to give methyl *cyclo*pentyl ketone semicarbazone, m. p. and mixed m. p. 144—145·5°, and with 2 : 4-dinitrophenylhydrazine to give the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 122·5—124°. Fraction (vii), which had n_D^{20} 1·4480, was identified as 2-methyl*cyclo*hexanone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 137—138°).

Comparison of the infra-red absorption spectra of fractions (iii)—(vii) with those of synthetic mixtures showed that the two ketones were present in the following proportions:

Fraction:	(iii)	(iv)	(v)	(vi)	(vii)
Methyl *cyclo*pentyl ketone, %	84	76	50	29	0
2-Methyl*cyclo*hexanone, %	16	24	50	71	100

1-*Phenyl*cyclo*hexene*. The olefin (40 c.c.) was treated with nitrous oxide at 300°/500 atm. for 3 hours, and the combined products from four experiments (165 g.) were distilled *in vacuo*. The material boiling up to 200°/2 mm. (114·5 g.) was distilled to give fractions: (i) b. p. <84°/2 mm., 5·3 c.c.; (ii) b. p. 84°/2 mm., 15 c.c.; (iii) b. p. 84—102·5°/2 mm., 15 c.c.; (iv) b. p. 102·5—107·5°/2 mm., 37 c.c.; (v) b. p. 107·5—123°/2 mm., 6·5 c.c.; and (vi) b. p. 123°/2 mm., 5·3 c.c.

Fraction (ii) was substantially pure 1-phenyl*cyclo*hexene, and fractions (i) and (iii) also contained considerable amounts of the olefin. Fraction (iv) had n_D^{20} 1·5426 and was identified as cyclo*pentyl phenyl ketone* (Found: C, 83·0; H, 8·7. $C_{18}H_{16}O$ requires C, 82·75; H, 8·05%) [*p-nitrophenylhydrazone*, m. p. 98° (Found: C, 70·0; H, 6·0; N, 13·6. $C_{18}H_{18}O_4N_2$ requires C, 69·9; H, 6·15; N, 13·6%); 2 : 4-*dinitrophenylhydrazone*, m. p. 143—144° (Found: N, 15·6. $C_{18}H_{18}O_4N_4$ requires N, 15·8%)]. Its structure was confirmed by degradation. Concentrated sulphuric acid (48 c.c.) was added to a stirred, ice-cooled solution of the ketone (12 g.) in chloroform (140 c.c.). Sodium azide (6 g.) was then added at 0—5° during 30 minutes. After a further 30 minutes' stirring the mixture was poured on ice, and the chloroform layer separated and washed with dilute sodium carbonate solution and with water. The chloroform was removed by distillation and the residue washed with pentane and crystallised from aqueous ethanol. This gave an amide (7·5 g.), m. p. 142—145°, which on further purification by solution in concentrated hydrochloric acid, and fractional precipitation by gradual addition of water, gave *N-cyclo*pentylbenzamide, m. p. and mixed m. p. 158—159°. The low m. p. of the crude amide was presumably attributable to the presence of a little of the isomeric *N*-phenyl*cyclo*pentanecarboxyamide, but its presence was not proved. Hydrolysis of the crude amide with concentrated hydrochloric acid at 200° gave as the main products benzoic acid, m. p. and mixed m. p. 122·5°, and *cyclo*pentylamine [*picryl* derivative, m. p. and mixed m. p. 105° (Found: N, 19·3. $C_{11}H_{13}O_7N_4$ requires N, 18·9%)].

Fraction (vi) was a solid which crystallised from light petroleum (b. p. 60—80°) to give 2-phenyl*cyclo*hexanone, m. p. 57° (Found: C, 82·7; H, 8·0. Calc. for $C_{12}H_{14}O$: C, 82·75; H, 8·05%) [oxime, m. p. 169° (Found: N, 7·35. Calc. for $C_{12}H_{15}ON$: N, 7·4%); semicarbazone, m. p. 179—181° (Found: N, 18·1. Calc. for $C_{13}H_{17}ON_3$: N, 18·2%)].

2-*Phenylpent*-2-*ene*. A solution of the olefin (20 c.c.) in *cyclo*hexane (20 c.c.) was treated with nitrous oxide at 280°/350 atm. for 4 hours. The product was fractionally distilled and in addition to *cyclo*hexane and unchanged olefin two main fractions were obtained. One of these, b. p. *ca.* 50°, was shown to contain propaldehyde [2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 155° (Found: N, 24·0. Calc. for $C_9H_{10}O_4N_4$: N, 23·6%)]. The other fraction, b. p. 68—74°/10 mm., was identified as acetophenone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 241—243·5°).

A small ketonic fraction, b. p. 85°/3 mm., was also obtained (Found: C, 81·6; H, 8·1. Calc. for $C_{11}H_{14}O$: C, 81·5; H, 8·65%). It formed a semicarbazone which, after recrystallisation from ethanol, had m. p. 183° (Found: N, 19·5. Calc. for $C_{12}H_{17}ON_3$: N, 19·2%).

2 : 3-*Dimethylbut*-2-*ene*. The olefin (40 c.c.) was treated with nitrous oxide at 300°/500 atm. for 4 hours, and the product distilled to give fractions: (i) b. p. 48—50°, 1 c.c.; (ii) b. p. 50—71°, 1·1 c.c.; (iii) b. p. 71—72°, 2·9 c.c.; (iv) b. p. 72—110°, 2 c.c.; and (v) b. p. 110—110·5°, 24 c.c.

Fraction (i) was identified as propaldehyde (dimethone, m. p. and mixed m. p. 153°); fraction (iii) was unchanged olefin; and fraction (v) was 2 : 2-dimethylbutan-3-one (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 125·5°; semicarbazone, m. p. and mixed m. p. 156—157°). No other products were detected.

The authors are indebted to Mr. F. Bebbington and Mrs. H. Malkin for assistance with the experimental work, and to Mr. L. H. Cross for the measurement and interpretation of the infra-red spectra.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, RESEARCH DEPARTMENT,
ALKALI DIVISION, NORTHWICH, CHESHIRE. [*Received, January 24th,* 1951.]

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668. *Oxidation of Organic Compounds by Nitrous Oxide. Part III.* Acetylenes.*

By G. D. BUCKLEY and (MISS) W. J. LEVY.

Acetylenic hydrocarbons react readily with nitrous oxide at 200—300°/100—500 atm. When the reaction is carried out in inert solvents the products are keten dimers, but carboxylic acids are formed in water, esters in alcohols, and amides in the presence of ammonia or amines. But-3-yn-1-ol reacts with nitrous oxide to give γ-butyrolactone, but βγ-acetylenic alcohols decompose under the conditions used.

It is thought that the primary product of the reaction of nitrous oxide with an acetylene is an α-diazo-ketone or α-diazo-aldehyde, which then loses nitrogen and undergoes anionotropic rearrangement to a ketene.

SINCE olefins react readily with nitrous oxide to give aldehydes and ketones (Part I), it was thought possible that acetylenes might react similarly to give ketens:

$$CR{\equiv}CH + N_2O \longrightarrow CHR{=}CO + N_2$$

Experiments showed that acetylenes did in fact react readily with nitrous oxide at 200—300°/100—500 atm., but, owing to the instability of the ketens under these conditions, it was usually desirable to carry out the reaction in the presence of substances which would rapidly combine with the keten to produce stable compounds. Thus nitrous oxide reacted with hex-1-yne in ethyl alcoholic solution to give a good yield of ethyl hexanoate; hept-1-yne similarly gave methyl heptanoate when it reacted in the presence of methanol, and *N-cyclo*hexylheptanoamide in the presence of *cyclo*hexylamine. Phenylacetylene reacted with nitrous oxide in ethanol to give ethyl phenylacetate, in water to give phenylacetic acid, and in an alcoholic solution of ammonia to give phenylacetamide. In inert solvents nitrous oxide reacted with hex-1-yne to give a compound, $C_{12}H_{20}O_2$, presumed to be butylketen dimer, and with phenylacetylene to give a tar from which no definite products could be isolated.

Disubstituted acetylenes behaved in a precisely similar manner:

$$CR{\equiv}CR + N_2O \longrightarrow CR_2{=}CO + N_2$$

Nitrous oxide reacted with dec-5-yne to give ethyl 2-butylhexanoate † in ethanol solution, and with diphenylacetylene to give methyl diphenylacetate in methanol solution and diphenylketen dimer in *cyclo*hexane solution.

Acetylene itself reacted with nitrous oxide in ethanol to give ethyl acetate and a trace of *n*-butaldehyde. The ester was presumably formed by the reaction of keten with ethanol but the source of the aldehyde is unknown; no aldehydes or ketones were detected in the reaction products from substituted acetylenes.

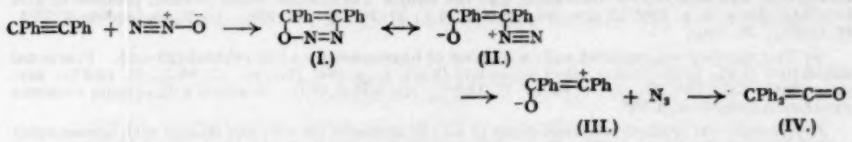
Diphenyldiacetylene apparently failed to react with nitrous oxide, and the product consisted of high-molecular weight hydrocarbons of an unknown nature. Attempts were also made to cause nitrous oxide to react with several hydroxyacetylenic compounds. But-3-yn-1-ol reacted readily with nitrous oxide in inert solvents to give γ-butyrolactone, presumably by formation and cyclisation of 2-hydroxyethylketen:

$$HO{\cdot}CH_2{\cdot}CH_2{\cdot}C{\equiv}CH + N_2O \longrightarrow HO{\cdot}CH_2{\cdot}CH_2{\cdot}CH{=}CO \longrightarrow \begin{matrix} CH_2{\cdot}CH_2{\cdot}CH_2 \\ O\text{———}CO \end{matrix}$$

On the other hand, βγ-acetylenic alcohols (propargyl alcohol, 2-methylbut-3-yn-2-ol, 1-phenylprop-2-yn-1-ol, and but-2-yn-1 : 4-diol) gave only complex mixtures of decomposition products.

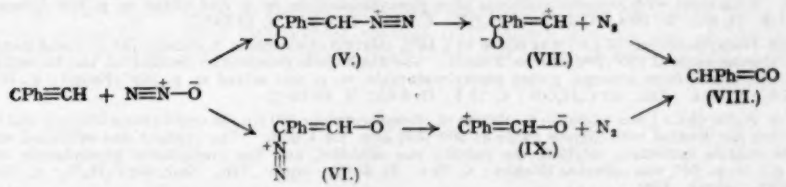
* Part II, preceding paper. † Geneva nomenclature, $CO_2H = 1$.

By analogy with the interpretation previously advanced for the reaction of nitrous oxide with olefins, it may be supposed that the initial step in the reaction of nitrous oxide with an acetylene is the formation of a 1 : 2 : 3-oxadiazole. Thus diphenylacetylene would yield 4 : 5-diphenyl-1 : 2 : 3-oxadiazole (I), which is merely a mesomeric form of α-diazodeoxybenzoin (II).



The thermal decomposition of (II) has been studied by Schroeter (*Ber.*, 1909, **42**, 2346, 3361) who found that it decomposed in boiling benzene to give diphenylketen (IV) and in boiling methanol to give methyl diphenylacetate. The formation of diphenylketen dimer by the reaction of nitrous oxide with diphenylacetylene and of methyl diphenylacetate in the presence of methanol is therefore consistent with the theory that (II) is formed as an intermediate. The initial step in the decomposition is presumably loss of nitrogen to form the unstable residue (III), which is then stabilised by anionotropic migration of the phenyl group.

A similar series of reactions must occur when acetylene itself and the monosubstituted acetylenes react with nitrous oxide. Phenylacetylene may react to give either ω-diazoacetophenone (V) or the unknown α-diazophenylacetaldehyde (VI) :



Elimination of nitrogen from (V) leaves the residue (VII) which may be expected to rearrange to phenylketen (VIII) by migration of the phenyl anion; (VIII) may similarly be formed from (VI) by loss of nitrogen and migration of the hydrogen anion.

The products isolated from the interaction of phenylacetylene and nitrous oxide in the presence of water, alcohol, and ammonia are consistent with this interpretation. The decomposition of ω-diazoacetophenone at low temperatures to give phenylketen or its addition products takes place only in the presence of a silver catalyst or under alkaline conditions (Arndt and Eistert, *Ber.*, 1935, **68**, 200). In neutral or acid media in the absence of the catalyst nitrogen is eliminated, but the residue (VII) reacts further without rearrangement. Thus the diazoketone decomposes in water at 70—80° to give ω-hydroxyacetophenone by direct addition of water to (VII) (Arndt and Amende, *Ber.*, 1928, **61**, 1122), and in boiling di*iso*amyl ether it gives 1 : 2 : 3-tribenzoyl*cyclo*propane, which is a trimer of (VII) (Grundmann, *Annalen*, 1938, **536**, 29). It must be assumed that, at the high temperature used in the nitrous oxide reaction, the rearrangement takes place even in the absence of a catalyst.

This work is the subject of B.P. Applns. 10026 and 10027/49.

Experimental.

Microanalyses are by Dr. A. F. Colson, and infra-red spectrography by Mr. L. H. Cross. All m. p.s are corrected.

Reaction of Acetylenes with Nitrous Oxide.—The apparatus and procedure were as described in Part I.

Acetylene. Acetylene (7·5 g.) was dissolved in ethanol (40 c.c.) at −50° and the vessel was then closed and heated to 300°. Nitrous oxide was admitted until the pressure was 500 atm. and the mixture was stirred under these conditions for 1 hour. The product had sap. value 169, equivalent to an ester content of 26·5% calculated as ethyl acetate, *i.e.*, 41% conversion. The solution was distilled and gave a fraction, b. p. 71·4—72·5°, which had sap. value 435, equivalent to 68·4% of ethyl acetate. According to Horsley (*Ind. Eng. Chem. Anal.*, 1947, **19**, 508) ethyl acetate and ethanol form an azeotrope, b. p. 71·8°, containing 69·2% of the ester. Reaction of this fraction with *o*-phenylenediamine gave 2-methylbenziminazole, characterised as the picrate, m. p. 212° (Found : N, 19·1. Calc. for $C_8H_8N_2.C_6H_3O_7N_3$: N, 19·35%).

The higher-boiling fraction, consisting mainly of unreacted ethanol, gave a small amount of *n*-butaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 123°, on treatment with 2 : 4-dinitrophenylhydrazine and hydrochloric acid.

Hex-1-yne. (*a*) A solution of hex-1-yne (7 c.c.) in *cyclo*hexane (33 c.c.) was treated with nitrous oxide at 300°/500 atm. for 1 hour. After the vessel had been cooled the pressure was released, the *cyclo*hexane was removed by distillation, and the residue was distilled under reduced pressure to give *butylketen dimer*, b. p. 170°/12 mm. (Found : C, 73·7; H, 10·2%; *M*, 238. $C_{12}H_{20}O_2$ requires C, 73·5; H, 10·2%; *M*, 196).

(*b*) The reaction was repeated with a solution of hex-1-yne (4 c.c.) in ethanol (36 c.c.). Fractional distillation of the product gave ethyl hexanoate (3 g.), b. p. 164° (Found : C, 66·5; H, 10·9%; sap. value, 394. Calc. for $C_8H_{16}O_2$: C, 66·65; H, 11·1%; sap. value, 389). Reaction with aqueous ammonia gave hexanoamide, m. p. 99°.

Hept-1-yne. (*a*) A solution of hept-1-yne (5 c.c.) in methanol (35 c.c.) was treated with nitrous oxide at 200°/300 atm. for 1 hour. The infra-red absorption spectrum of the resulting solution showed a band at 5·79 μ., characteristic of the carbonyl group; this was attributed to the presence of methyl heptanoate, and the ester content of the solution was calculated from the intensity of this band; the conversion was 8·5%.

The experiment was repeated at 250° (conversion 57·0%) and again at 300° (conversion 87·0%).

(*b*) A mixture of hept-1-yne (10 c.c.) and *cyclo*hexylamine (20 c.c.) was treated with nitrous oxide at 250°/500 atm. for 1 hour. The crude product was triturated with dilute hydrochloric acid, collected, and washed with water. There remained crude N-cyclo*hexylheptanoamide* (30·5 g.; 94% of theory), which crystallised from aqueous ethanol in plates, m. p. 82—83° (Found : C, 73·7; H, 11·8; N, 6·4. $C_{13}H_{25}ON$ requires C, 73·95; H, 11·85; N, 6·65%).

Phenylacetylene. (*a*) A solution of phenylacetylene (6·5 g.) in ethanol (33·5 c.c.) was treated with nitrous oxide at 300°/500 atm. for 1 hour. The product was fractionally distilled, giving ethyl phenylacetate (3·5 g.), b. p. 226—228°, n_D^{20} 1·4983 (Found : sap. value, 341. Calc. for $C_{10}H_{12}O_2$: sap. value, 338). Treatment with aqueous ammonia gave phenylacetamide, m. p. and mixed m. p. 158° (Found : C, 71·2; H, 6·7; N, 10·4. Calc. for C_8H_9ON : C, 71·1; H, 6·65; N, 10·35%).

(*b*) Phenylacetylene (5 c.c.) was added to a 16% solution of ammonia in ethanol (35 c.c.) and treated with nitrous oxide at 250°/200 atm. for 2 hours. The alcohol was removed by distillation, and the residue was crystallised from benzene, giving phenylacetamide, m. p. and mixed m. p. 159° (Found : C, 70·9; H, 7·0; N, 10·1. Calc. for C_8H_9ON : C, 71·1; H, 6·65; N, 10·35%).

(*c*) Water (5 c.c.) was added to a solution of phenylacetylene (10 c.c.) in *cyclo*hexane (25 c.c.) and the mixture was treated with nitrous oxide at 300°/500 atm. for 1 hour. The product was extracted with dilute sodium carbonate solution, the extract was acidified, and the precipitated phenylacetic acid (2·0 g.), m. p. 76°, was collected (Found : C, 70·4; H, 5·9%; equiv., 140. Calc. for $C_8H_8O_2$: C, 70·6; H, 5·9%; equiv., 136).

Dec-5-yne. A solution of dec-5-yne (8 c.c.) in ethanol (32 c.c.) was treated with nitrous oxide at 300°/500 atm. for 1 hour. After removal of the alcohol by distillation the residue was fractionally distilled under reduced pressure. This gave ethyl 2-butylhexanoate, b. p. 90—95°/6 mm., n_D^{20} 1·4240 (Found : C, 72·3; H, 11·7%; sap. value, 286. Calc. for $C_{12}H_{24}O_2$: C, 72·0; H, 12·0%; sap. value, 280). Reaction with ammonia gave 2-butylhexanoamide, m. p. 135°. Levene and Cretcher (*J. Biol. Chem.*, 1918, **33**, 508) give b. p. 114—115°/15 mm. for the ester, and Dolique (*Ann. Chim.*, 1941, **15**, 425) gives m. p. 134·5° for the amide.

Diphenylacetylene. (*a*) Diphenylacetylene (15 g.) and *cyclo*hexane (25 c.c.) were treated with nitrous oxide at 300°/500 atm. for 1 hour. The product was a dark brown solution which deposited a solid. The solid, apparently a diphenylketen dimer (14 g.; 87% of theory), was collected, washed with *cyclo*hexane, and recrystallised from acetic acid to give crystals, m. p. 173° (Found : C, 87·2; H, 5·1%; *M*, 400. Calc. for $C_{28}H_{20}O_2$: C, 86·6; H, 5·15%; *M*, 388). Staudinger (*Ber.*, 1911, **44**, 530) describes a polymer, m. p. 176°, of diphenylketen.

(*b*) Diphenylacetylene (10 g.) and methanol (30 c.c.) were treated with nitrous oxide at 300°/500 atm. for 1 hour. The solid product was collected and crystallised from methanol, giving methyl diphenylacetate, m. p. 57—58° (Found : C, 79·8; H, 6·3%; sap. value, 253. Calc. for $C_{15}H_{14}O_2$: C, 79·65; H, 6·2% sap. value, 243). Hydrolysis gave diphenylacetic acid, m. p. 148—149° (Found : C, 79·1; H, 6·1. Calc. for $C_{14}H_{12}O_2$: C, 79·2; H, 5·65%).

But-3-yn-1-ol. A solution of but-3-yn-1-ol (4·3 g.) in *cyclo*hexane (35 c.c.) was treated with nitrous oxide at 300°/300 atm. for 1 hour. The *cyclo*hexane was removed by distillation and the residue was distilled under reduced pressure. This gave γ-butyrolactone (3·2 g.), b. p. 49—50°/3 mm., 204—206°/760 mm., n_D^{20} 1·4353 (Found : C, 55·5; H, 7·2%; sap. value, 608. Calc for $C_4H_6O_2$: C, 55·8; H, 7·0%; sap. value, 651). Reaction with phenylhydrazine gave γ-hydroxybutyric phenylhydrazide, m. p. and mixed m. p. 92—93°.

The authors are indebted to Professor E. R. H. Jones and Mr. J. D. Rose for samples of various acetylenic compounds, and to Mr. F. Bebbington and Mrs. H. Malkin for assistance with the experimenta work described above.

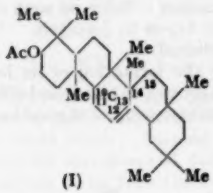
IMPERIAL CHEMICAL INDUSTRIES LIMITED, RESEARCH DEPARTMENT,
ALKALI DIVISION, NORTHWICH, CHESHIRE.

669. *Triterpene Resinols and Related Acids. Part XXII.** iso-β-*Amyrenonol and* iso-β-*Amyradienonol.*

By Richard Budziarek, J. D. Johnston, William Manson, and F. S. Spring.

The reactions of the enol acetate of *iso*-β-amyrenonyl acetate show that the parent αβ-unsaturated ketone is correctly formulated as 2-acetoxyolean-10-en-12-one (VI). *iso*-β-Amyrin acetate, derived from *iso*-β-amyrenonyl acetate by catalytic or Clemmensen reduction, is shown to be 2-acetoxyolean-10-ene (IX) and it is concluded that the locking of rings B/C in β-amyrin corresponds to the more stable configuration. It is shown that Clemmensen reduction of *iso*-β-amyradienonyl acetate gives β-amyradienyl-II acetate (XVIII), and this and other reactions of *iso*-β-amyradienonyl acetate are discussed.

Oxidation of β-amyrin acetate (I) with hydrogen peroxide gives the saturated ketone β-amyranonyl acetate (II) (Spring, *J.*, 1933, 1345; Picard, Sharples, and Spring, *J.*, 1939, 1045). The amorphous solid obtained from the reaction mixture after the removal of β-amyranonyl acetate yielded an acetate $C_{32}H_{52}O_4$ which does not exhibit selective absorption of high intensity in the ultra-violet region and cannot be acetylated under normal conditions but is hydrolysed by alkali to the corresponding alcohol $C_{30}H_{50}O_3$. Of the structures (III) and (IV) which appear probable for this, the former was excluded since the acetate is stable to chromic anhydride at room temperature whereas (III) should give the enol of 2-acetoxy-oleanane-11 : 12-dione (Ruzicka and Jeger, *Helv. Chim. Acta*, 1941, **24**, 1178).


Me
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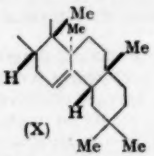
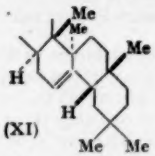
around $C_{(10)}$ * (cf. the catalytic reduction of β-amyranonol to β-amyrin described by Ruzicka and Jeger, *loc. cit.*, 1941). Of the alternative structures (IX) and (XI) for the isomeric β-amyrin acetate, the former has been established by Kishner–Wolff reduction of the derived isomeric β-amyranonyl acetate to a product which after acetylation gave β-amyranyl acetate (XII)

(IX)



(X)



(XI)

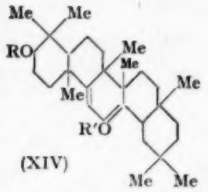
identical with the compound obtained by similar treatment of β-amyranonyl acetate (Ruzicka and Jeger, *loc. cit.*, 1941). The isomeric β-amyranonyl acetate is therefore 2-acetoxyoleanan-11-one (XIII). An interesting point concerning the nature of the locking of rings B/C in the β-amyrin group of triterpenoids emerges from this series of changes. The conversion of β-amyrin into 2-acetoxyoleanan-11-one (XIII) and thence into β-amyranyl acetate (XII) proves that these rings are locked in the more stable configuration since the introduction of a carbonyl group at the 11-position and the subsequent treatment of this ketone would permit

(XII)

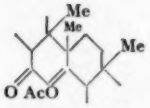
(XIII)

the change from a less to a more stable configuration at this junction. Since no such isomerisation occurs it is concluded that the more stable configuration exists in β-amyrin. Whether the more stable configuration is *cis* or *trans* remains to be established.

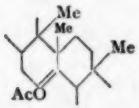
In an attempt further to characterise *iso*-β-amyrenonol by the formation of its benzoate, it was treated with benzoyl chloride and pyridine. The product proved to be an enol dibenzoate which gives a brown colour with tetranitromethane and exhibits selective absorption in the



(XIV)



(XV)

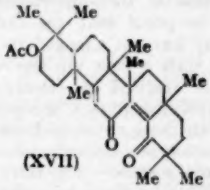


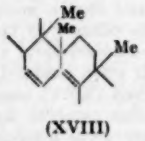
(XVI)

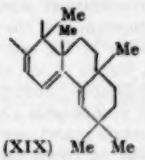
ultra-violet with maxima at 2300 Å (ε = 31,000) attributable to the two benzoyl groups and at 2750 Å (ε = 11,000) attributable to a diene system present in a single ring. The enol dibenzoate is therefore (XIV; R = R′ = COPh), and the structure of *iso*-β-amyrenonyl acetate as 2-acetoxyolean-10-en-12-one (VI) is confirmed. Treatment of *iso*-β-amyrenonyl acetate with acetic anhydride and sodium acetate gives an enol acetate (XIV; R = R′ = Ac) which exhibits an absorption maximum at 2780 Å characteristic of a conjugated diene system present in a single ring. The enol acetate grouping is easily hydrolysed with the re-formation of *iso*-β-amyrenonyl acetate. The structure (XIV; R = R′ = Ac) was supported by oxidation of the 10-ethylenic linkage of the enol acetate with hydrogen peroxide, with formation of 2-acetoxyoleanane-11 : 12-dione enol acetate (XV; R = Ac) previously obtained by Ruzicka and Jeger (*loc. cit.*, 1941) by chromic acid oxidation of the enol acetate of β-amyranonyl acetate (XVI; R = Ac). Two other oxidation products were obtained from the enol acetate (XIV; R = R′ = Ac) : selenium dioxide in acetic acid gave *iso*-β-amyradienonyl acetate, and *N*-bromosuccinimide in carbon tetrachloride gave, surprisingly, β-amyradienedionyl acetate (XVII).

* The configurations shown in (X) and (XI) are for the most part arbitrary and are used for comparative purposes only. The *cis*-locking of rings D/E, however, has been established by Barton and Holness (*Chem. and Ind.*, 1951, 233; Davy, Halsall, and Jones, *ibid.*, p. 233).

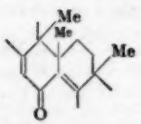
β-Amyradienedionyl acetate is obtained by the oxidation of β-amyrin acetate (I) (Jeger and Ruzicka, *Helv. Chim. Acta*, 1941, **24**, 1236), β-amyradienyl-I acetate (VII) (Picard and Spring, *J.*, 1941, 35), β-amyradienyl-II acetate (XVIII) (Ruzicka, Jeger, and Norymberski, *Helv. Chim. Acta*, 1942, **25**, 457; Barton and Brooks, *J.*, 1951, 257), and β-amyratrienyl acetate (XIX) (Newbold and Spring, *J.*, 1944, 532) with selenium dioxide; we find that

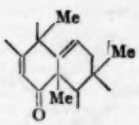

(XVII)

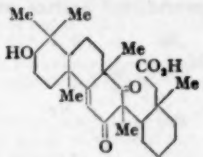

(XVIII)


(XIX)

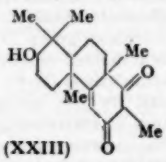
oxidation of *iso*-β-amyrin acetate (2-acetoxyolean-10-ene) (IX) with selenium dioxide also gives β-amyradienedionyl acetate. The interpretation of the complex reactions of β-amyradienedionyl acetate and of analogous compounds obtained from other members of the β-amyrin group of triterpenoids by Ruzicka and Jeger has provided weighty evidence in favour of part of the detail of the formula (I) for β-amyrin acetate. *iso*-β-Amyrenonyl acetate (VI) contains half of the chromophore of β-amyradienedionyl acetate (XVII) and accordingly

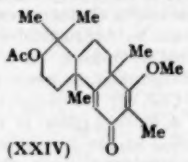

(XX)

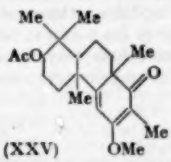

(XXI)


(XXII)

Green, Mower, Picard, and Spring (*loc. cit.*) attempted to correlate these two compounds by oxidation of the former with selenium dioxide in the expectation that β-amyradienedionyl acetate would result. Instead, the reaction gave *iso*-β-amyradienonyl acetate which shows an absorption maximum at 2450 Å (ε = 10,000) and unlike *iso*-β-amyrenonyl acetate gives a yellow colour with tetranitromethane. *iso*-β-Amyradienonyl acetate was also obtained by the action of bromine on *iso*-β-amyrenonyl acetate by the same workers and by Jeger and


(XXIII)

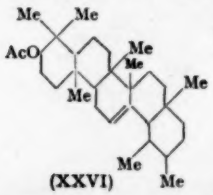

(XXIV)

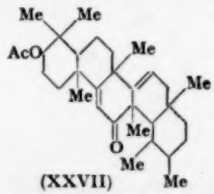

(XXV)

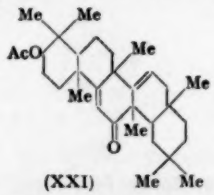
Ruzicka (*loc. cit.*, 1945); *iso*-β-amyradienonyl acetate can also be obtained directly from β-amyranonyl acetate by bromination. Green, Mower, Picard, and Spring (*loc. cit.*) suggested the structure (XX) for *iso*-β-amyradienonyl acetate, whereas Jeger and Ruzicka proposed the structure (XXI) in which it is represented as formed from *iso*-β-amyrenonyl acetate by the migration of the angular methyl group from $C_{(14)}$ to $C_{(13)}$ with simultaneous introduction of a 14 : 15-double bond. More recently Meisels, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1950, **33**, 700) have oxidised *iso*-β-amyradienonyl acetate to a hydroxy-diketo-acid formulated as (XXII), the methyl ester of which on pyrolysis gave an acidic fraction represented as the hydroxy-diketone (XXIII). The hydroxy-diketone was characterised by methylation and acetylation which gave two isomeric compounds formulated as (XXIV) and (XXV) and identical with two compounds obtained by, in all essential features, the same route starting from α-amyrin. These reactions cannot be construed as *proof* of migration of the angular methyl group during conversion of *iso*-β-amyrenonyl acetate into *iso*-β-amyradienonyl acetate.

We find that Clemmensen reduction of *iso*-β-amyradienonyl acetate gives β-amyradienyl-II acetate (XVIII) which contains the same carbon skeleton as β-amyrin. In itself this reaction

can be reconciled with the structure (XXI) for *iso*-β-amyradienonyl acetate by assuming that the strongly acid medium induces a second migration of the angular methyl group at $C_{(13)}$ to its original position at $C_{(14)}$, thus giving the dienone (XX), Clemmensen reduction of which would yield β-amyradienyl-II acetate. It was noted, however, that *iso*-β-amyradienonyl acetate was recovered unchanged after prolonged treatment with hydrochloric acid in acetic acid. On the other hand, the conversion of *iso*-β-amyradienonyl acetate into β-amyradienyl-II acetate could be considered to be proof that the carbon skeleton of both compounds is the same and that a methyl group has not changed its place during the conversion of the one into the other. In favour of such a view are the following very substantial facts: first, that *iso*-α-amyrenonyl acetate is oxidised by selenium dioxide to *iso*-α-amyradienonyl acetate which when oxidised and pyrolysed gives a product from which are isolated compounds (XXIV) and (XXV) identical with those obtained from *iso*-β-amyradienonyl acetate; and, secondly, that catalytic hydrogenation of *iso*-α-amyradienonyl acetate in acetic acid at room temperature gives *iso*-α-amyrenonyl acetate. The latter observation proves that *iso*-α-amyradienonyl acetate has the same carbon skeleton as α-amyrin and that *iso*-α-amyradienonyl acetate does not carry a methyl group at $C_{(13)}$ (McLean, Ruff, and Spring, *J.*, 1951, 1093). The conversion of both *iso*-α-amyradienonyl acetate and *iso*-β-amyradienonyl acetate into the compounds (XXIV) and (XXV) requires that *iso*-β-amyradienonyl acetate likewise does not carry such a methyl group. In marked contrast to the behaviour of *iso*-α-amyradienonyl acetate, *iso*-β-amyradienonyl acetate is reduced catalytically in acetic acid at room temperature with absorption of two molecular proportions of hydrogen and formation of *iso*-β-amyradienyl acetate which differs from each of the previously described isomers.

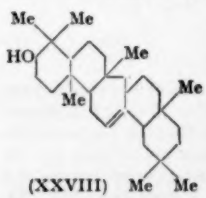

(XXVI)


(XXVII)


(XXI)

iso-β-Amyradienyl acetate does not show selective absorption in the ultra-violet region, yet it gives an intense red colour with tetranitromethane in chloroform; within our experience this is the first example of a triterpene which does not contain a conjugated system of ethylenic bonds giving an intense red or brown colour with this reagent. This acetate is not isomerised by mineral acid. The carbonyl group of *iso*-β-amyradienonyl acetate is reduced by lithium aluminium hydride; the resulting diene-diol is characterised as its diacetate, catalytic reduction of which gives *iso*-β-amyradienyl acetate by hydrogenolysis of the acetoxy-group in ring C.

Our conclusions may be summarised as follows. A series of well-defined reactions of the α- and the β-amyrin group has been interpreted in terms of the formulations (I) for β-amyrin acetate and (XXVI) for α-amyrin acetate, by the assumption of migration of a methyl group in the changes *iso*amyrenonol ⟶ *iso*-amyradienonol. In the α-amyrin series the postulated migration is demonstrably incorrect since simple catalytic reduction of *iso*-α-amyradienonyl acetate yields the parent *iso*-α-amyrenonyl acetate. In the β-amyrin series, the postulated migration also appears unlikely (but not excluded) since *iso*-β-amyradienonol can be converted by Clemmensen reduction into a well-known derivative of β-amyrin which possesses the same carbon skeleton as the latter. The conversion of the *iso*-α- and the *iso*-β-amyradienonyl acetate into two common degradation products which apparently include the rings A—C of the triterpenes, suggests that in so far as these rings are concerned, the α- and β-amyradienonyl acetates have identical carbon skeletons; since (XXVII) is not an acceptable formulation for *iso*-α-amyradienonyl acetate, (XXI) for *iso*-β-amyradienonyl acetate is suspect. An attractive hypothesis to circumvent the anomalies described above is that neither α- nor β-amyrin carries a methyl group attachment at $C_{(14)}$ (cf. Jeger, Rüegg, and Ruzicka, *Helv. Chim. Acta*, 1947, **30**, 1294); in such an event the accommodation of the displaced carbon atom becomes a matter for speculation. The possibility that ring C is 7-membered (β-amyrin = XXVIII) (cf. Meyer, Jeger, Prelog, and Ruzicka, *Helv. Chim. Acta*, 1951, **34**, 747) has been considered by us for some


(XXVIII)

time, together with alternative methods for the accommodation of the carbon atom displaced from $C_{(14)}$. Such speculations are premature since the views expressed above are to a large measure dependent on the validity of the interpretation of the reactions leading from the *iso*-dienonyl acetates to the compounds (XXIV) and (XXV) and in particular on the validity of the structures ascribed to the last two compounds, which in our opinion require substantiation.

Experimental.

M. p. s are corrected; those taken on a Kofler block are marked (K). Specific rotations were measured at 15—20° in chloroform solutions in a 1-dm. tube.

β-Amyranonyl Acetate.—The following variation of the method described by Spring (*loc. cit.*) has been developed after many attempts to improve the yield of this intermediate. β-Amyrin acetate (m. p. 238—239°; 20 g.) in glacial acetic acid (1800 c.c.) was treated at 100° with a mixture of hydrogen peroxide (100-vol.; 150 c.c.) in glacial acetic acid (150 c.c.) added dropwise during 30 minutes with stirring. Stirring was continued for 2 hours at 100° and the solution again treated with hydrogen peroxide (100-vol.; 50 c.c.) in acetic acid (50 c.c.) during 15 minutes. The solution was kept at 100° for 1 hour and hot water was added until the mixture became faintly opalescent. The crystalline solid separating overnight was collected (m. p. 288—291°; 8·7 g.). The mother-liquor was heated to 100°, then treated with hot water until opalescent, and a second crop isolated (m. p. 286—287°; 2·0 g.). The two crops were combined, dissolved in light petroleum (b. p. 60—80°)–benzene (1 : 2; 300 c.c.), and purified by chromatography on an alumina column (Grade I/II, 46 × 3·5 cm.). Washing with the same solvent mixture (3450 c.c.) gave an eluate (7·05 g.) which when recrystallised from chloroform–methanol yielded β-amyranonyl acetate as plates, m. p. 300—301° (K) (299—300° in an open capillary), $[\alpha]_D$ −15° (*c*, 2·82), −15° (*c*, 5·83) (Found: C, 79·0; H, 10·7. Calc. for $C_{32}H_{52}O_3$: C, 79·3; H, 10·8%). Continued washing of the column successively with light petroleum (b. p. 60—80°)–benzene (1 : 4; 600 c.c.), benzene (600 c.c.), and benzene–ether (19 : 1) gave fractions (total, 1·3 g.), crystallisation of which from chloroform–methanol gave β-amyranonyl acetate, m. p. 299—300°, $[\alpha]_D$ −15°.

Hydrolysis of β-amyranonyl acetate by 3% alcoholic potassium hydroxide gave β-amyranonol as prisms (from aqueous acetone), m. p. 205—206°, $[\alpha]_D$ −26° (*c*, 2·77), acetylation of which gave β-amyranonyl acetate, m. p. 299—300°, $[\alpha]_D$ −15° (*c*, 2·50).

Acetate, $C_{32}H_{52}O_4$. After removal of the two crystalline crops from the "perhydrol" oxidation mixture, further dilution with water gave an amorphous solid. The liquor was poured into water and the solid collected. Attempted crystallisation of this solid was not successful. A solution of the dry amorphous solid (20 g.; obtained from the oxidation of 50 g. of β-amyrin acetate) in light petroleum (b. p. 60—80°)–benzene (3 : 1; 500 c.c.) was filtered through a column of activated alumina (Grade II/III, 40 × 3·5 cm.), and the column eluted with light petroleum–benzene (3 : 1). Fraction 1 (from 400 c.c.) was discarded. Fraction 2 (from 250 c.c.), thrice recrystallised from ethanol, gave β-amyranonyl acetate, m. p. and mixed m. p. 289—291° (0·7 g.). Fraction 3 (from 700 c.c.), recrystallised from ethanol to m. p. <280° and then from methanol, gave an *acetate* as prismatic needles, m. p. 288—289°, $[\alpha]_D$ +28·6° (*c*, 0·56) (Found: C, 76·5, 76·4; H, 10·5, 10·4. $C_{32}H_{52}O_4$ requires C, 76·75; H, 10·5%). A mixture with β-amyranonyl acetate had m. p. 263—273°. This acetate does not give a colour with tetranitromethane in chloroform or with aqueous alcoholic ferric chloride. The acetate was recovered unchanged after treatment (*a*) with acetic acid–hydrogen bromide at room temperature for 3 days, (*b*) in benzene–acetic acid (1 : 9) with chromic anhydride (1·5 atoms of O) in acetic acid for 20 hours at room temperature, or (*c*) with bromine in acetic acid at 80°.

Attempted purification of other fractions from the chromatogram did not give homogeneous material.

Alcohol, $C_{30}H_{50}O_3$. A solution of the acetate (100 mg.) in alcoholic potassium hydroxide (3%; 5 c.c.) was refluxed for 3 hours. Isolation of the product by means of ether, followed by three crystallisations from methanol, gave the *alcohol* (60 mg.) as prisms, m. p. 249—250°, $[\alpha]_D$ +19·6° (±1·5°) (*c*, 1·33) (Found: C, 77·7; H, 11·2. $C_{30}H_{50}O_3$ requires C, 78·4; H, 11·0%). The alcohol separates from methanol with solvent of crystallisation which it retains tenaciously. When heated in a vacuum the substance disintegrates with loss of solvent which is complete only after three sublimations at 10^{-2} mm. and 180—210°, 210—230°, and 220—240° respectively. After this treatment the m. p. is unaltered.

The alcohol with pyridine–acetic anhydride gave the acetate $C_{32}H_{52}O_4$ as needles (from methanol), m. p. 292—293°, $[\alpha]_D$ +28·4° (*c*, 1·48), undepressed in m. p. when mixed with the acetate described above.

iso-*β-Amyrenonyl Acetate.*—This was prepared essentially as described by Picard, Sharples, and Spring (*loc. cit.*) except that the reaction was carried out at higher dilution (*e.g.*, 2·2 g. of β-amyranonyl acetate in 220 c.c. of acetic acid) and the bromine was reduced to 1·1—1·3 mols. After the bromination was complete, the solution was kept at room temperature for approx. 20 hours. To ensure that the dehydrohalogenation of the intermediate bromo-ketone (Seymour and Spring, *loc. cit.*) is complete, it is advisable to precipitate the reaction mixture with water, collect, wash, and dry the crude reaction product, and reflux a solution of this in acetic acid for 1 hour. Addition of boiling water to this solution gave *iso*-β-amyrenonyl acetate as hexagonal plates, m. p. 289—290°, $[\alpha]_D$ +62° (*c*, 1·33). Other preparations had m. p. 289—290°, $[\alpha]_D$ +61° (*c*, 1·15), m. p. 287—289°, $[\alpha]_D$ +60° (*c*, 2·2), and chromatography on alumina (Grade II) gave a specimen, m. p. 289—290°, $[\alpha]_D$ +60° (*c*, 2·3) (Found: C, 79·6; H, 10·4. Calc. for $C_{32}H_{50}O_3$: C, 79·6; H, 10·45%).

Hydrolysis of the acetate (purified by chromatography) gave *iso*-β-amyrenonol as prisms (from methanol), m. p. 249—250°, $[\alpha]_D$ +57·5° (*c*, 1·55). Acetylation by acetic anhydride–pyridine gave the acetate as plates (from acetone), m. p. 290—291·5°, $[\alpha]_D$ +61·5° (*c*, 1·40).

Enol Benzoate of iso-*β*-*Amyrenonyl Benzoate*.—A solution of *iso*-*β*-amyrenonol (90 mg.) in pyridine (1 c.c.) was treated with 3 drops of benzoyl chloride, and the mixture heated at 100° for 4 hours. The product, isolated by means of ether in the usual manner, crystallised from acetone–methanol (1 : 1) as plates (65 mg.), m. p. 225·5—227°. After four recrystallisations from methanol the *enol benzoate* was obtained as plates, m. p. 235—235·5°, $[\alpha]_D$ +246° (*c*, 1·22) (Found: C, 81·1; H, 8·4. $C_{44}H_{66}O_4$ requires C, 81·4; H, 8·6%). Light absorption in ethanol: Max. at 2300 (ε = 31,000) and 2750 Å (ε = 11,000). The enol benzoate gives a red-brown colour with chloroformic tetranitromethane.

Enol Acetate of iso-*β*-*Amyrenonyl Acetate*.—A solution of *iso*-*β*-amyrenonyl acetate (1·0 g.) in acetic anhydride (60 c.c.) containing freshly fused sodium acetate (0·5 g.) was heated under reflux for 80 hours. The reaction mixture was treated with water and extracted with ether. The extract was washed with water, shaken with charcoal, and dried (Na_2SO_4). After removal of the ether the residue crystallised from chloroform–methanol, to give the *enol acetate* (0·85 g.) as prismatic needles, m. p. 216·5—217°, $[\alpha]_D$ +201° (*c*, 1·60) (Found: C, 77·5; H, 9·9. $C_{34}H_{52}O_4$ requires C, 77·8; H, 9·9%). Light absorption in ethanol: Max. at 2780 Å (ε = 8500). The enol acetate gives a brown colour with tetranitromethane in chloroform. The enol ester group is easily hydrolysed, attempted purification by chromatography on alumina giving *iso*-*β*-amyrenonyl acetate in quantitative yield. The enol acetate was recovered unchanged after treatment with bromine in glacial acetic acid at 60°.

Enol Acetate of 2-*Acetoxyoleanane*-11 : 12-*dione*.—A solution of the enol acetate of *iso*-*β*-amyrenonyl acetate (0·3 g.) in acetic acid (20 c.c.) was treated with vigorous stirring at 100° with 10 c.c. of a solution of hydrogen peroxide (30%; 25 c.c.) in acetic acid (25 c.c.). After 1 hour a second addition of the peroxide–acetic acid mixture (20 c.c.) was made, stirring continued for 2 hours, and the remainder of the peroxide solution added. After a further hour the solution was diluted with water, and the solid collected and crystallised from chloroform–methanol, giving the enol acetate of 2-acetoxyoleanan-11 : 12-dione as flat needles, m. p. 228—229°, $[\alpha]_D$ +80° (*c*, 1·50). The compound does not give a colour with tetranitromethane in chloroform and exhibits an absorption maximum at 2550 Å (ε = 10,900). A specimen prepared by oxidation of the enol acetate of *β*-amyranonyl acetate as described by Ruzicka and Jeger (*loc. cit.*, 1941) separated from chloroform–methanol as flat prismatic needles, m. p. 233—234° (K), $[\alpha]_D$ +78° (*c*, 1·2), exhibited an absorption maximum (in alcohol) at 2550 Å (ε = 11,200), and was undepressed in m. p. when mixed with the specimen obtained by the oxidation of the enol acetate of *iso*-*β*-amyrenonyl acetate.

β-*Amyradienedionyl Acetate*.—A solution of the enol acetate of *iso*-*β*-amyrenonyl acetate (0·4 g.) and *N*-bromosuccinimide (0·5 g.), in dry carbon tetrachloride was heated under reflux for 8 hours, during which the solution developed a deep yellow colour and hydrogen bromide was evolved. The filtered solution was evaporated to dryness, and the residue triturated with warm water. The solid was collected, dried, and twice crystallised from aqueous methanol, yielding *β*-amyradienedionyl acetate as square plates, m. p. 237—238° (K), $[\alpha]_D$ −95° (*c*, 0·25), giving a negative reaction with tetranitromethane and showing an absorption maximum (in alcohol) at 2780 Å (ε = 10,000). When mixed with a specimen obtained by the oxidation of *β*-amyrin acetate with selenium dioxide {m. p. 236—237°, $[\alpha]_D$ −94° (*c*, 1·73)} there was no depression in m. p.

2-*Acetoxyolean*-10-*ene*.—*iso*-*β*-Amyrenonyl acetate (0·30 g.) in acetic acid (80 c.c.) containing concentrated hydrochloric acid (15 c.c.) was treated with amalgamated zinc (9 g.) and kept at 100° for 6 hours during which additions of concentrated hydrochloric acid (5 c.c.) were made at two-hourly intervals. The hot solution was decanted into water, and the solid collected, washed, dried, and crystallised from methanol–chloroform, to yield a crystalline solid (155 mg.), m. p. 240—255°. The solid was readily separated by chromatography of a light petroleum–benzene solution (4 : 1; 50 c.c.) on activated alumina (Grade II, 14 × 1·5 cm.) into a fraction I (94 mg.) eluted by light petroleum–benzene (4 : 1; 200 c.c.) and a fraction II (53 mg.) eluted by benzene (150 c.c.). Crystallisation of fraction I from chloroform–methanol gave 2-acetoxyolean-10-ene as plates, m. p. 250—251°, $[\alpha]_D$ +77° (*c*, 0·3) (Found: C, 82·1; H, 11·4. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%). A mixture with a specimen of the isomeric *β*-amyrin acetate {plates from methanol–chloroform; m. p. 250—251°, $[\alpha]_D$ +77° (*c*, 1·64)} prepared by the catalytic hydrogenation of *iso*-*β*-amyrenonyl acetate (Jeger and Ruzicka, *loc. cit.*, 1945) showed no depression in m. p. Crystallisation of fraction II from chloroform–methanol gave *iso*-*β*-amyrenonyl acetate as plates, m. p. 285—286° undepressed when mixed with a specimen of the starting material.

β-*Amyranyl Acetate*.—2-Acetoxyoleanan-11-one [plates from chloroform–methanol; m. p. 338—339° (evacuated tube)] was prepared as described by Jeger and Ruzicka (*loc. cit.*, 1945). A solution of the keto-acetate (250 mg.) and hydrazine (100%; 2 c.c.) in ethanolic sodium ethoxide (7·5%; 10 c.c.) was kept at 200—210° for 18 hours in an autoclave. The acetylated reaction product (85 mg.) was dissolved in light petroleum (b. p. 60—80°)–benzene (2 : 1; 50 c.c.) and filtered through a column of alumina (Grade II, 10 × 1·25 cm.). Washing with the same solvent mixture (50 c.c.) gave a fraction (30 mg.), crystallisation of which from chloroform–methanol yielded *β*-amyranyl acetate as plates, m. p. 282—284°, $[\alpha]_D$ +24° (*c*, 0·46), undepressed when mixed with a specimen prepared by reduction of *β*-amyranonyl acetate as described by Ruzicka and Jeger (*Helv. Chim. Acta*, 1941, **24**, 1178).

iso-*β*-*Amyradienonyl Acetate*.—(a) *Selenium dioxide method*. Oxidation of *iso*-*β*-amyrenonyl acetate ($[\alpha]_D$ +60°; 1 g.) was effected as described by Green, Mower, Picard, and Spring (*loc. cit.*) with the difference that the period of reflux was 48 hours. The hot mixture was filtered and the solution diluted with water. The solid was collected, washed, and dried. A solution of the solid in ether was washed with 5% aqueous potassium cyanide. After being washed with water and freed from ether, the solid crystallised from acetone as plates, m. p. 208—216°. Recrystallisation again gave plates, m. p. 212—213°, but a third crystallisation from the same solvent gave prisms (0·3 g.), m. p. 220—221°, not altered in crystalline form or in m. p. by further crystallisation. After sublimation at 180—190°/10^{-3} mm., *iso*-*β*-amyradienonyl acetate had m. p. 220—221·5°, $[\alpha]_D$ −38·3° (*c*, 1·07) (Found: C, 79·6; H, 9·9.

Calc. for $C_{31}H_{48}O_2$: C, 80·0; H, 10·1%). By combination and concentration of mother-liquors, a further crop (0·2 g.) of *iso*-β-amyradienonyl acetate was obtained having m. p. 217—218·5°.

In another experiment, the crude reaction product separated as plates, m. p. 202—204°, from aqueous alcohol. When this material was recrystallised from acetone, large plates separated which were kept overnight in contact with its mother-liquor. The plates had then changed into prisms, m. p. 215—217·5°. Recrystallisation from the same solvent gave *iso*-β-amyradienonyl acetate as prisms which when dried for a week in a vacuum over phosphoric oxide at 135° had m. p. 220—221°, $[\alpha]_D$ −39·8° (*c*, 1·32). Light absorption in ethanol: Max. at 2450 Å (ε = 10,100) with an inflection at 3400 Å.

(b) *Bromine method.* β-Amyrananonyl acetate (1·9 g.; m. p. 292°) in glacial acetic acid (150 c.c.) was treated with a solution of bromine in glacial acetic acid (8%; 2·1 mols.) during 5 minutes at 90°. The solution was kept at 90° for 1 hour and then overnight at room temperature. The mixture was diluted with water, and the solid collected, washed, dried, and crystallised from acetone. The first crop (0·34 g.) separated as plates, m. p. 278—280°, which did not give a colour with tetranitromethane in chloroform and proved to be *iso*-β-amyrenonyl acetate. The second crop consisted of prisms contaminated with a small number of plates. The two forms were separated mechanically into plates (0·03 g.), m. p. 215—255°, giving no colour with tetranitromethane, and prisms (0·69 g.), m. p. 207—209°, $[\alpha]_D$ −25° (*c*, 2·1), which gave a yellow colour with tetranitromethane. Recrystallisation of the prisms from acetone gave prisms (0·56 g.), m. p. 214—217°. A solution of this solid (0·53 g.) in light petroleum (b. p. 60—80°)–benzene (5 : 1; 100 c.c.) was filtered through a column of activated alumina (Grade II, 15 × 2 cm.). Light petroleum (330 c.c.), followed by light petroleum–benzene (4 : 1; 220 c.c.), eluted *iso*-β-amyradienonyl acetate (400 mg.) which after crystallisation from acetone (prisms), followed by sublimation, had m. p. 218—219·5°, $[\alpha]_D$ −39·8° (*c*, 1·97) (Found: C, 80·0; H, 9·7. Calc. for $C_{32}H_{48}O_2$: C, 79·95; H, 10·1%).

(c) *From the enol acetate of* iso-β-*amyrenonyl acetate.* The enol acetate of *iso*-β-amyrenonyl acetate (0·45 g.; m. p. 216—217°) was refluxed in stabilised glacial acetic acid with selenium dioxide for 72 hours. Selenium was removed by filtration, the filtrate diluted with water, and the mixture extracted with ether. The extract was washed successively with water and 5% potassium cyanide solution. After drying ($MgSO_4$), the extract was evaporated to dryness and the residue (0·43 g.) fractionally crystallised from chloroform–methanol. The first two crops (0·34 g.) separated as needles, m. p. 215—216° undepressed when mixed with the enol acetate of *iso*-β-amyrenonyl acetate. The third crop (0·06 g.) separated as needles, m. p. 190—196°; it was thrice recrystallised from the same solvent, to give *iso*-β-amyradienonyl acetate as prisms, m. p. 218—219°, depressed to 180—195° when mixed with the enol acetate of *iso*-β-amyrenonyl acetate, and undepressed when mixed with a specimen of *iso*-β-amyradienonyl acetate prepared by method (a); it had $[\alpha]_D$ −39° (*c*, 0·70). Light absorption in ethanol: Max. at 2450 Å (ε = 11,200).

iso-β-*Amyradienonol.*—This was obtained by hydrolysis of the acetate (m. p. 219—220°; $[\alpha]_D$ −38°) with 3% alcoholic potassium hydroxide. It separates from methanol as large hard prisms, m. p. 241—242°, $[\alpha]_D$ −51° (*c*, 1·24). Reacetylation using pyridine and acetic anhydride gave *iso*-β-amyradienonyl acetate as prisms (from methanol), m. p. 220—221°, $[\alpha]_D$ −40° (*c*, 0·95).

A solution of *iso*-β-amyradienonol (80 mg.) in pyridine (1 c.c.) and benzoyl chloride (0·15 c.c.) was heated at 100° for 3 hours. The product, isolated in the usual manner, crystallised from methanol to give iso-β-*amyradienonyl benzoate*, m. p. 207—208°, $[\alpha]_D$ −23° (*c*, 0·80) (Found: C, 81·5; H, 9·0. $C_{37}H_{50}O_2$ requires C, 81·9; H, 9·3%).

Clemmensen Reduction of iso-β-*Amyradienonyl Acetate.*—A hot solution of *iso*-β-amyradienonyl acetate (prepared by the selenium dioxide method; 0·5 g.) in hot acetic acid (40 c.c.) was treated with concentrated hydrochloric acid (10 c.c.) and added to freshly amalgamated zinc (from 15 g. of zinc), and the mixture heated under reflux for 30 minutes. The product, isolated in the usual manner, separated from acetic acid as plates (220 mg.), m. p. 204—210°. It was recrystallised from acetone and then thrice from alcohol, to yield β-amyradienyl-II acetate as plates, m. p. 227—228°, $[\alpha]_D$ −61·8° (*c*, 2·08) (Found: C, 82·6; H, 10·6. Calc. for $C_{32}H_{50}O_2$: C, 82·3; H, 10·8%). It gives a red-brown colour with tetranitromethane in chloroform. Light absorption in alcohol: Max. at 2515 (ε = 28,200), 2435 (ε = 24,700), and 2600 Å (ε = 18,000). A mixture with a specimen (m. p. 227—228°) prepared by selenium dioxide oxidation of β-amyrin acetate had m. p. 227—228°.

iso-β-*Amyradienyl Acetate.*—(*a*) A solution of *iso*-β-amyradienonyl acetate (200 mg.; m. p. 220°) in glacial acetic acid (50 c.c.) was added to a suspension of freshly reduced platinum catalyst (from 100 mg. of platinum oxide) in glacial acetic acid (10 c.c.) and the mixture shaken with hydrogen at 16°. Absorption of hydrogen was at first rapid, and after 45 minutes approximated to 1 mol. After 44 hours the apparent absorption of hydrogen was between 2 and 3 mols. The product, isolated in the usual manner and crystallised repeatedly from methanol, gave iso-β-*amyradienyl acetate* as feather-like crystals, m. p. 225—226°, $[\alpha]_D$ +5·2° ±1° (*c*, 1·95) (Found: C, 82·0; H, 11·2. $C_{32}H_{50}O_2$ requires C, 82·3; H, 10·8%). *iso*-β-Amyradienyl acetate gives a red-brown colour with chloroformic tetranitromethane and does not exhibit selective absorption in the ultra-violet region.

(*b*) A solution of *iso*-β-amyradienonyl acetate (400 mg.) in ether (50 c.c.) was added dropwise to a suspension of lithium aluminium hydride (300 mg.) in ether (40 c.c.). The mixture was refluxed for 4 hours, treated with water, and acidified with dilute sulphuric acid. The ethereal solution was separated, washed, dried, and evaporated. The product was acetylated by warming it with acetic anhydride (0·5 c.c.) in pyridine (3 c.c.) for 3 hours; crystallisation from aqueous methanol then gave the *diacetate* (360 mg.) as square plates, m. p. 167—168°, $[\alpha]_D$ +25·4° (*c*, 1·0) (Found: C, 78·0; H, 10·05. $C_{34}H_{52}O_4$ requires C, 77·8; H, 10·0%). The diacetate gives a yellow colour with tetranitromethane in chloroform and does not exhibit selective absorption of appreciable intensity in the ultra-violet region.

A solution of the diacetate, m. p. 167—168° (100 mg.), in glacial acetic acid (20 c.c.) was added to a suspension of a freshly reduced platinum catalyst (from 100 mg. of platinum oxide) in glacial acetic acid (100 c.c.) and the mixture shaken with hydrogen for 20 hours. The product was isolated in the usual manner and crystallised from methanol, to give *iso*-β-amyradienyl acetate as needles, m. p. 223—224°, $[\alpha]_D$ +5·3° (*c*, 0·95), giving a red colour with tetranitromethane and showing no selective absorption in the ultra-violet region. A mixture with a specimen m. p. 225° prepared by method (*a*) had m. p. 224—225°.

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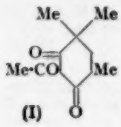
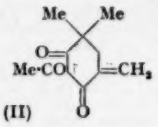
670. β-*Triketones. Part I. The Structures of Angustione, Dehydroangustione, Calythrone, and Flavaspidic Acid.*

By ARTHUR J. BIRCH.

New formulæ are advanced for angustione (I),* dehydroangustione (II), calythrone (III),* and flavaspidic acid (XX), chiefly on the basis of published evidence assisted by some spectra and model reactions.

VARIOUS alkali-soluble substances have been isolated from plants which owe their acidity to the presence of three carbonyl groups attached to the same methine group. Among those about which considerable information is available are: leptospermone (IV) (Briggs, Hassall, and Short, *J.*, 1945, 706; Briggs, Hassall, and Taylor, *J.*, 1948, 383); calythrone, formulated as (V) by Penfold and Simonsen (*J.*, 1940, 412); angustione and dehydroangustione, formulated as (VI) and (VII) respectively (Gibson, Penfold, and Simonsen, *J.*, 1930, 1184; Cahn, Gibson, Penfold, and Simonsen, *J.*, 1931, 286); humulone and lupulone (Wöllmer, *Ber.*, 1925, **58**, 672; Wieland and Martz, *Ber.*, 1926, **59**, 2352); usnic acid (Curd and Robertson, *J.*, 1937, 898); and a number of substances from male-fern, among them albaspidin (XXI) and flavaspidic acid which was formulated as (XVII) (Boehm, *Annalen*, 1898, **302**, 171; 1899, **307**, 250; 1901, **318**, 230 *et seq.*; 1903, **329**, 310). Most of these substances have biological activity and they include anthelmintics, insecticides, and antibiotics.


(I)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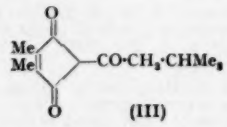
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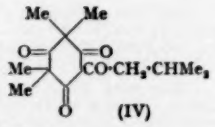
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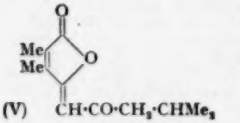
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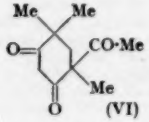
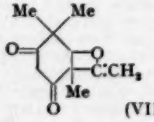

(VI)

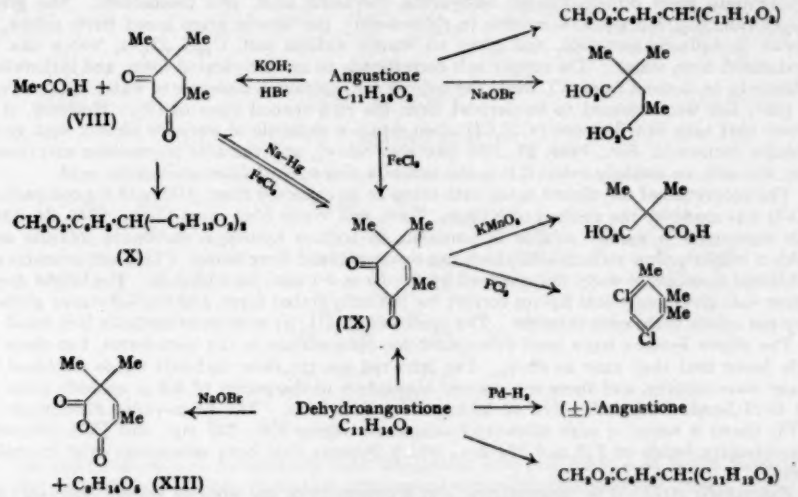

(VII)

Angustione and Dehydroangustione.—Angustione, $C_{11}H_{14}O_3$, and dehydroangustione, $C_{11}H_{14}O_3$, occur in admixture in the oil of *Backhousia angustifolia* and are separated with some difficulty by crystallisation of their imines, from which they can be regenerated with alkali (Simonsen *et al.*, *locc. cit.*). They give intense orange-red colours with ferric chloride and form copper salts which are soluble in some organic solvents. They react with one molecule of reagents such as hydroxylamine, phenylhydrazine, or semicarbazide with elimination of two molecules of water. Their principal transformations are shown in the annexed scheme.

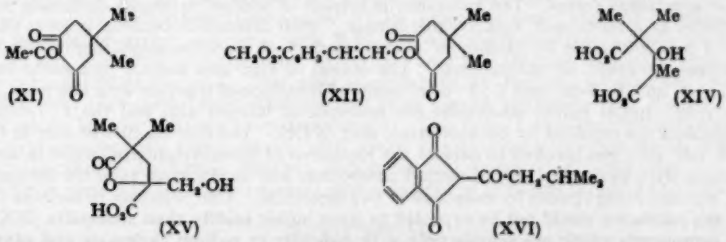
There seems little doubt that (VIII) and (IX) are correctly formulated. They both react with piperonaldehyde in the manner characteristic of *cyclo*hexane-1 : 3-diones in the proportion of two molecules of ketone to one of aldehyde, giving products of the type (X). Angustione and dehydroangustione on the contrary give condensation products in molar proportions, which throws doubt on formulæ (VI) and (VII) since the $CO{\cdot}CH_2{\cdot}CO$ system should be

* Professor C. H. Hassall informs the author that he has independently derived the same formulæ for these two substances.

the reactive one (compare the action of formaldehyde on butanofilicinic acid; Boehm, *loc. cit.*). A study of the reaction of (XI) with piperonaldehyde showed that it forms a compound, similar to the derivatives of angustione and dehydroangustione, and formulated as (XII) since it is soluble in alkali and gives a deep brown colour with ferric chloride. Furthermore, copper salts and ferric colours of any intensity are not to be expected from (VI) and (VII) because the 1 : 3-diketo*cyclo*hexane system, although highly enolised, is *trans* and incapable of chelation; 5 : 5-dimethyl*cyclo*hexane-1 : 3-dione (dimedon) does not in fact show this behaviour. The reactions and properties of substances such as (XI) are closely similar to those of angustione and dehydroangustione (cf. Dieckmann and Stein, *Ber.*, 1904, **37**, 3370; Crossley and Renouf, *J.*, 1912, **101**, 1529): they give deep ferric colours, form bright blue copper salts soluble in chloroform, produce anhydro-derivatives with ketone reagents like hydroxylamine, and form crystalline imines from which they can be regenerated by alkali. The infra-red absorption spectrum of (XI) is very similar to those of angustione and dehydroangustione, showing in particular a series of strong bands in the region 6—7·5 μ. probably connected with the ketonic groupings and related structures. There seems little doubt that (I) correctly represents angustione, and its synthesis by standard methods is in hand.



Some difficulties remain in formulating dehydroangustione. It is obviously very closely related to angustione, and the presence in the infra-red absorption of a strong band at 11·75 μ. and an indication of a peak at 6·1 μ (partly obscured by the carbonyl band at 5·95 μ.) points to a >C:CH₂ group in the molecule. Formula (II) is therefore highly probable, but it contains



no asymmetric centre, and dehydroangustione is reported to be optically active. The rotation is low, however, and of the same sign as that of angustione, and Cahn *et al.* (*loc. cit.*) have pointed out that their dehydroangustione probably contained 20—25% of angustione. Another difficulty is the nature of the substance (XIII) obtained in the hypobromite oxidation. This was

formulated as (XIV) on the basis of its reduction with hydriodic acid to αα*γ*-trimethylglutaric acid, and the closeness of its melting point (156—157°) to that (154—156°) reported by Perkin and Smith (*J.*, 1903, 776) for (XIV). However, if dehydroangustione is optically active, as was assumed on the basis of (VII), then (XIV) should also be optically active and its melting point is not a good criterion of comparison with the (±)-acid of Perkin and Smith. The compound was found to titrate as a monobasic acid in cold solution, and as a dibasic acid only with hot alkali. A more likely formulation is (XV), derived from (II), which would require $C_8H_{12}O_5$ instead of $C_8H_{14}O_5$. The ready conversion of itaconic acid into citraconic anhydride shows that a bond migration of the type required to give trimethylglutaconic anhydride might readily occur; similarly the formation of (IX) could easily occur through bond shift. If dehydroangustione is in fact optically active the only likely alternative formulation involves the presence of a *cyclo*propane ring. The parachors calculated on the basis of (I) and (II) are both about twenty units higher than the values found (Evans and Soper, *J.*, 1931, 289), but such anomalies are frequent with hydrogen-bonded substances. On the old formulæ angustione showed the anomaly and dehydroangustione did not.

Calythrone.—Calythrone, $C_{13}H_{16}O_3$, from the oil of *Calythrix tetragona*, on oxidation with hypobromite gives dimethylmaleic anhydride, *iso*valeric acid, and bromoform. The green copper salt, $(C_{13}H_{15}O_3)_2Cu$, is soluble in chloroform; the ketone gives a red ferric colour, is soluble in aqueous ammonia, and gives an orange sodium salt, $C_{13}H_{17}O_4Na$, which can be crystallised from water. The copper salt corresponds to an unhydrated form, and is therefore unlikely to be derived from (V), while the sodium salt contains a molecule of water not removed at 100°, and was assumed to be derived from the ring-opened form of (V). However, it is known that salts of triketones $(\cdot CO)_2CH$ often retain a molecule of water or alcohol with great tenacity (Schwerin, *Ber.*, 1894, **27**, 104) (see also below), and the acid regenerates calythrone from the salt, an unlikely event if it is the salt of a ring-opened diketocarboxylic acid.

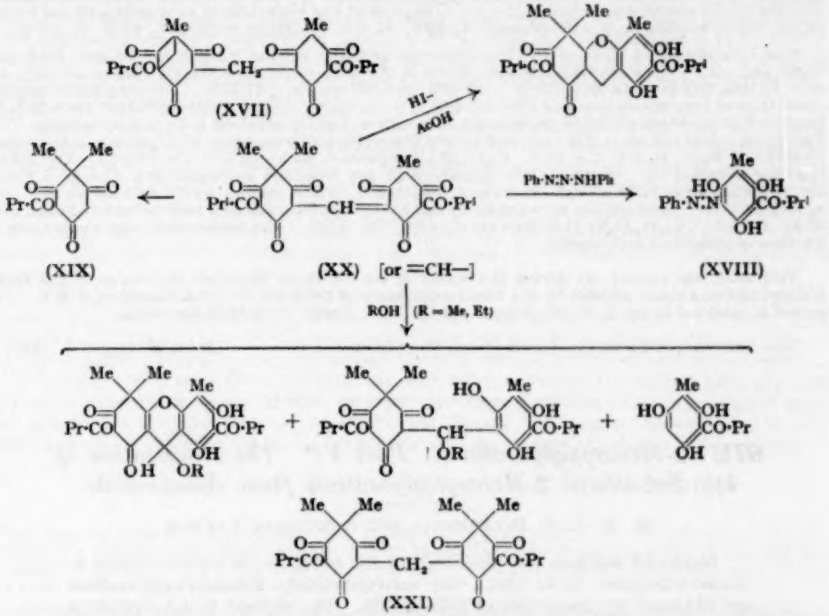
The properties of calythrone agree with those to be expected from (III), and for comparison (XVI) was made by the method of Kilgore, Ford, and Wolfe (*Ind. Eng. Chem.*, 1942, **34**, 494). This compound is readily soluble in ammonia or sodium hydrogen carbonate solution and yields a bright yellow sodium salt which can be crystallised from water. This salt contains an additional molecule of water not removed by drying at 0·1 mm. for 48 hours. The bright green copper salt gives analytical figures correct for the unhydrated form, and the substance gives a deep red colour with ferric chloride. The synthesis of (III) by analogous methods is in hand.

The above ketones have been formulated for convenience in the keto-forms, but there is little doubt that they exist as enols. The infra-red spectra show carbonyl bands displaced to longer wave-lengths, and there is a general absorption in the region of 3·3 μ. on both sides of the C–H band, both indicative of hydrogen-bonded enols. The ultra-violet absorption of (XVI) shows a series of high intensity bands in the region 230—320 mμ., and (XI) possesses high-intensity bands at 273 and 231 mμ., which indicate that both substances exist in enolic forms.

Flavaspidic Acid.—The thoroughness and competence of the work of Boehm (*locc. cit.*) on the constituents of male-fern have tended to obscure the fact that his structures for substances such as flavaspidic acid (XVII) and filicic acid, although undoubtedly correct in general outline are far from certainly established in detail. Flavaspidic acid, $C_{24}H_{28}O_6$, is a yellow substance existing in two forms, which are readily interconvertible but apparently are not just different crystalline forms. The substance is soluble in sodium hydrogen carbonate solution and titrates as a monobasic acid towards litmus. With diazoaminobenzene it gives (XVIII), a type of reaction shown by Boehm to be characteristic of methylenediphloroglucinols having all positions occupied by substituents. The action of zinc and sodium hydroxide leads to mono-, 1 : 1- and 1 : 3-di-, and 1 : 3 : 5-tri-methylphloroglucinol together with two molecules of butyric acid; under milder conditions one molecule of butyric acid and the 1 : 1-dimethylphloroglucinol are replaced by butanofilicinic acid (XIX). The four-membered ring in (XVII) (Boehm, *locc. cit.*) was invoked to explain the formation of trimethylphloroglucinol in amounts comparable with the mono- and di-methyl compounds and at the same time the formation of (XIX), the ring being opened by reduction in two directions. One objection to formula (XVII) is that the substance would not be expected to show higher acidity than albaspidin (XXI) and similar compounds which are soluble only with difficulty in sodium carbonate and cannot be titrated with litmus. There is also no explanation of the bright yellow colour, since albaspidin and similar compounds are colourless. A more likely formulation on the evidence available is (XX) the methine bridge giving rise to quinonoid properties. The two forms may then arise owing to the ready shift of the double bond from one nucleus to the other, although in the

pyrromethene series this shift is so easy that such isomers have not been isolated, and in a system with so many tautomeric possibilities other explanations are possible. The other transformations shown below are much more rationally formulated on the new than on the old formula, especially the addition of alcohols, a type of reaction known to occur with pyrromethenes and methylenequinones (cf. Zincke, *Annalen*, **1903**, **329**, 61). The exact structures of the xanthen derivatives depend on the unknown direction of ring-closure.

A similar formula can also be assigned to filicic acid; this will be considered in a later communication.



The chief difficulty in formulating both flavaspidic acid and filicic acid is the formation, by zinc and alkali reduction, of notable amounts of trimethylphloroglucinol, which, however, may be explicable on the basis of (XX) on the following grounds. It can be assumed that the first stage of the reduction is the formation of the methylenediphloroglucinol derivative of the type R–CH_2–R′ and these are known to undergo reactions in which R^- or R'^- appear—the reductive fission is one example—the negative charge being stabilised by resonance forms in which it appears on an oxygen atom. Equilibria of the type R–CH_2–R′ + H_2O ⇌ R·CH_2·OH + R′H are therefore likely to be set up, especially under alkaline conditions, the reverse reaction occurring, not only with R′H, but also with products already formed by reduction, *e.g.*, dimethylphloroglucinol. In the last case the ultimate reduction product will contain trimethylphloroglucinol. This view is supported by Boehm's observation (*Annalen*, **1903**, **329**, 269) that methylenediphloroglucinol gives rise on reduction, not only to methyl- and dimethyl-, but also to trimethyl-phloroglucinol. This type of equilibrium also explains the ready disproportionation which occurs with many unsymmetrical pyrromethenes and with rottlerin (Backhouse, McGookin, Matchet, Robertson, and Tittensor, *J.*, 1948, 113).

Synthetic work is in hand in connection with a number of problems raised in this paper.

Experimental.

2-Acetyl-5 : 5-dimethylcyclohexane-1 : 3-dione.—This was prepared according to Crossley and Renouf (*loc. cit.*) and purified through its copper salt. The ultra-violet absorption (in ethanol) shows bands at 273 (ε = 10,800) and 231 mμ. (ε = 10,620). The infra-red absorption bands are recorded below, together with those of angustione and dehydroangustione taken from curves kindly supplied by Professor Sir John Simonsen, F.R.S.

Strong bands, 3·43, 6·0, 6·39, 6·93, 9·55, 10·55 μ.; medium bands; 8·10, 8·73, 8·90, 10·25, 10·82 μ.; weak bands, 11·25, 12·2, 14·2 μ.; side-bands, 7·05, 7·12, 7·20, 7·30, 7·50, 7·77, 7·96, 8·6, 9·73 μ.

Angustione: strong bands, 3·35, 5·95, 6·4, 6·95, 8·2, 8·55, 9·7, 10·08 μ.; medium bands, 8·92, 9·95, 10·6, 11·2, 11·5 μ.; weak bands, 12·2, 12·9, 13·6 μ.; side-bands, 7·2, 7·3, 7·43, 7·60, 8·0 μ.

Dehydroangustione: strong bands, 3·35, 5·95, 6·08, 6·45, 6·95, 7·7, 8·05, 8·54, 9·72, 9·95, 10·63, 11·30 μ.; medium bands, 8·75, 10·35, 11·87, 1272 μ.; weak bands, 13·5, 14·1 μ.; side-bands, 3·41, 7·2, 7·34, 8·94, 11·41 μ.

The *piperonylidene* derivative was obtained by heating 2-acetyl-5 : 5-dimethyl*cyclo*hexane-1 : 3-dione (100 mg.) with piperonaldehyde (200 mg.) and piperidine (20 mg.) on the steam-bath for 30 minutes, followed by the addition of methanol (2 c.c.). The product was recrystallised from methanol and formed bright yellow needles, m. p. 116° (Found: C, 69·0; H, 5·8. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%).

2-iso*Valerylindane*-1 : 3-*dione* (XVI).—This was prepared by the method of Kilgore, Ford, and Wolfe (*loc. cit.*). It showed the following bands in the ultra-violet (in ethanol): 323 (ε = 8170), 311 (ε = 11,150), 283 (ε = 32,680), 274 (ε = 22,800), and 237 mμ. (ε = 17,270). The infra-red absorption curve showed very strong bands at 5·85 and 6·09 μ. in the region of normal carbonyl bands and a broader band at 6·29 μ. which probably corresponds to a carbonyl group involved in hydrogen-bonding. The dark green *copper* salt, m. p. 274°, was best crystallised by partial evaporation of its solution in chloroform (Found: C, 64·0; H, 5·3; Cu, 11·9. $C_{28}H_{34}O_6Cu$ requires C, 64·3; H, 5·0; Cu, 12·2%). The *sodium* salt was obtained by dissolving the substance in hot N-sodium carbonate and cooling, followed by recrystallisation from water. It formed long bright yellow needles which sintered at 200° and melted at 215°. After drying at 0·1 mm. for 48 hours it still contained 1 mol. of water (Found: C, 62·0; H, 5·45. $C_{14}H_{13}O_3Na,H_2O$ requires C, 62·2; H, 5·5%. The combustion was carried out in presence of potassium dichromate).

This work was carried out during the tenure of the Smithson Research Fellowship of the Royal Society, and was made possible by the kind co-operation of Professor Sir John Simonsen, F.R.S. The author is indebted to Dr. S. F. MacDonald and Dr. W. I. Taylor for helpful discussions.

THE UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, July 27th*, 1951.]

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671. 2-*Mercaptoglyoxalines. Part V.* The Preparation of 4(5)-Substituted 2-Mercaptoglyoxalines from Amino-acids.*

By R. A. F. BULLERWELL and ALEXANDER LAWSON.

Improved methods are described for the reduction of α-amino-esters to amino-aldehydes, from which the correspondingly 2-mercaptoglyoxalines are obtained by the action of thiocyanate. The method is not entirely a general one; it has been successful with all amino-acids used except cysteine, threonine, tryptophan, and valine.

THE effectiveness of 2-mercaptoglyoxaline and its substitution products in inhibiting thyroxine synthesis by the thyroid gland (Stanley and Astwood, *Endocrinol.*, 1949, **44**, 588; Searle, Lawson, and Morley, *Biochem. J.*, 1951, **49**, 125) has evoked considerable interest in their synthesis (Jones, Kornfeld, McLaughlin, and Anderson, *J. Amer. Chem. Soc.*, 1949, **71**, 4000). One of the simplest methods of wide application for the preparation of 4(5)-substituted derivatives is the action of thiocyanic acid on α-amino-aldehydes which, as Neuberg (*Ber.*, 1908, **41**, 959) showed, could be obtained by the reduction of esters of α-amino-acids by sodium amalgam. This reaction was employed later by Akabori (*Ber.*, 1933, **67**, 151, 159) who described the reduction of ethyl esters of a limited number of amino-acids and the subsequent production of the corresponding 2-mercaptoglyoxalines.

To improve the somewhat variable, low yields (particularly in the case of glycine) obtained by the Akabori procedure and so facilitate the use of these compounds as starting material for further synthetic work, a study has been made of this reduction, with an extended range of amino-acids. The method cannot be considered an entirely general one since a uniform procedure is not applicable in all cases, and furthermore with cysteine, threonine, tryptophan, and valine no yield of the corresponding mercaptoglyoxaline has so far been isolated.

The use of solid carbon dioxide as an internal cooling agent during the reduction of the amino-acid esters has been described in Part II (*J.*, 1951, in the press). By this means the

* Part IV, *J.*, 1951, 2223.

optimum temperature of reduction (0°) can be steadily maintained and the time of addition of the amalgam and hence the risk of hydrolysis of the ester reduced.

The α-amino-aldehydes obtained by reduction are not stable in alkaline solution and as the pH optimum for the reduction is between 2 and 3 a fairly strict control of the pH during the reduction is necessary.

These pH and temperature conditions, whilst proving advantageous in the case of alanine were, however, not in themselves satisfactory with glycine, serine, and histidine, in particular. With glycine, the isolation of the 2-mercaptoglyoxaline still required the laborious separation as the mercuric chloride complex and its subsequent decomposition with hydrogen sulphide. With serine and histidine no yield of the corresponding mercaptoglyoxalines was obtained. These difficulties were to a large extent overcome by carrying out the reduction in the presence of thiocyanate. It is possible that as soon as the labile amino-aldehyde is formed it undergoes the first stage of its reaction with thiocyanic acid to give the substituted thiourea which then cyclises when the solution is boiled.

It has been shown by Dixon and Taylor (*J.*, 1916, **109**, 1244) that thiourea in cold aqueous solution reacts with acetaldehyde to give a type of Schiff's base, from which the aldehyde can be regenerated by boiling it with acids. The use of thiourea to protect the amino-aldehyde was therefore examined in the case of glycine ester. The result was successful, although the hope that the thiourea would, on subsequent treatment, decompose to liberate enough thiocyanic acid to bring about ring closure was not realised, and the yield of mercaptoglyoxaline (22%) obtained after the addition of thiocyanate was restricted by the difficulty of separation from the thiourea.

Coppin and Titherly (*J.*, 1914, **105**, 32) have described the reversible formation of 2 : 2 : 2-trichloro-1-hydroxyethylurea from chloral and urea. The use of the latter compound as a temporary stabilising agent for the amino-aldehydes has proved most advantageous, and in the case of glycine ester 35—40% yields were obtained without the use of mercuric chloride.

It has been found difficult to crystallise the more soluble mercaptoglyoxalines from solutions containing appreciable excess of thiocyanates. In the preparation of 2-mercaptoglyoxaline and 4-hydroxymethyl-2-mercaptoglyoxaline from glycine and serine, respectively, it was therefore found desirable to use only a little more than the theoretical amount of thiocyanate.

Experimental.

2-Mercaptoglyoxaline.—Glycine ester hydrochloride (10 g.) was dissolved in ice-cold water (50 ml.). The solution was efficiently stirred and kept at 0° by the addition of small pieces of solid carbon dioxide; potassium thiocyanate (7 g.) was then added, followed by freshly prepared sodium amalgam (2·3%, 300 g.) in small portions during 45 minutes.

Throughout the reaction, the pH of the solution was kept at approximately 2·3 by addition of 5N-hydrochloric acid (60 ml.) from a dropping funnel. When all the hydrochloric acid had been used, the solution was decanted from the mercury, filtered, and boiled under reflux for 40 minutes. It was then evaporated to dryness under reduced pressure and the residue was extracted with ethanol. After removal of the alcohol, the product was crystallised from boiling water; it had m. p. 225—227° (yield 2·8 g., 33%). By carrying out the reduction in the presence of urea (5 g.) and postponing the addition of the thiocyanate till all the sodium amalgam had been used, a purer product was isolated in 40% yield.

2-Mercapto-4-methylglyoxaline.—DL-Alanine (18 g.) was suspended in absolute ethanol (300 ml.), which had been previously saturated with dry hydrogen chloride, and the mixture heated on the water-bath until all had passed into solution. Benzene (100 ml.) was then added and the solvents were removed by distillation under reduced pressure. The semi-solid residue, together with potassium thiocyanate (40 g.) was dissolved in ice-cold water (100 ml.), the pH being adjusted to 2·3 and the temperature kept at 0° by means of solid carbon dioxide. Sodium amalgam (2·3%, 600 g.) was used under the conditions described for the reduction of glycine ester. The resulting solution was boiled under reflux for 30 minutes and concentrated until the product began to crystallise. Evaporation of the mother liquor to dryness followed by extraction with ethanol gave more material. The product had m. p. 246° (total yield 12·8 g., 55%).

2-Mercapto-4-propylglyoxaline.—When the same method as that described for alanine was used, DL-norvaline (5 g.) gave 2-mercapto-4-propylglyoxaline (3·9 g., 64%). After recrystallisation from water the needles had m. p. 183—184°.

4-n-Butyl-2-mercaptoglyoxaline.—DL-Norleucine (5 g.) treated as above gave *4-butyl-2-mercapto-glyoxaline* (2·0 g., 34%). Recrystallisation from water gave needles, m. p. 127·5°, sparingly soluble in cold water but soluble in ethanol (Found: C, 53·2; H, 7·7. $C_7H_{12}N_2S$ requires C, 53·8; H, 7·7%).

Di-(2-mercapto-4-glyoxalinyl)methane.—αγ-Diaminoglutaric acid (5 g.), obtained by the method described by Carter *et al.* (*J. Biol. Chem.*, 1949, **178**, 331) and treated as above, gave *di-(2-mercapto-4-*

glyoxalinyl)methane (2·1 g., 32%). The compound did not melt below 300°. It was soluble in ethanol and concentrated hydrochloric acid, and recrystallised from the latter solvent in pale yellow needles (Found: C, 38·8; H, 3·8. $C_7H_8N_4S_2$ requires C, 39·6; H, 3·8%).

2-Mercapto-4-glyoxalinylacetic Acid.—DL-Aspartic acid (5 g.), treated as above, yielded *2-mercapto-4-glyoxalinylacetic acid* (3·25 g., 71%), which crystallised from water as pale yellow needles, m. p. 245°, which were slightly soluble in cold water, more so in ethanol (Found: C, 37·9; H, 4·1. $C_5H_6O_2N_2S$ requires C, 38·0; H, 3·8%). When heated at 210°, slight darkening occurred and carbon dioxide was evolved, giving 4-methyl-2-mercaptoglyoxaline, mixed m. p. 245°.

4-p-Hydroxybenzyl-2-mercaptoglyoxaline.—L-Tyrosine (5 g.) reacted in the manner described above to give *4-p-hydroxybenzyl-2-mercaptoglyoxaline* (2·5 g., 44%). Recrystallised from ethanol, the compound had m. p. 248° (Found: C, 58·1; H, 5·0; N, 12·8; S, 14·5. $C_{10}H_{10}ON_2S$ requires: C, 58·3; H, 4·9; N, 13·6; S, 15·5%). It was sparingly soluble in water and ethanol.

4-4′-Aminobutyl-2-mercaptoglyoxaline.—DL-Lysine monohydrochloride (5 g.) was esterfied and reduced as in the case of alanine except that a smaller quantity of potassium thiocyanate (3 g.) was used. The resulting solution was heated on the water-bath for 1 hour and was then adjusted to pH 6 by the addition of dilute ammonia solution. Evaporation to dryness was carried out under reduced pressure, and the product was isolated after an extraction with ethanol. Recrystallisation from water gave *4-4′-aminobutyl-2-mercaptoglyoxaline hydrochloride* (1·7 g., 30%), m. p. 214° (Found: C, 40·1; H, 6·8; N, 19·7. $C_7H_{13}N_3S,HCl$ requires C, 40·5; H, 6·7; N, 20·2%). The hydrochloride (1·2 g.) was dissolved in a little water and N-sodium hydroxide (5·8 ml.) was added. The free *base* separated, and after being recrystallised from water had m. p. 123° (Found: C, 49·1; H, 7·5. $C_7H_{13}N_3S$ requires C, 49·1; H, 7·6%).

4-4′-Glyoxalinylmethyl-2-mercaptoglyoxaline.—The methyl ester hydrochloride obtained from L-histidine (5 g.) was treated in the same way as glycine ester hydrochloride with two modifications: the solution of the amino-aldehyde and thiocyanate was heated on the water-bath for 1 hour instead of being boiled under reflux, and the pH was brought to 6·0 before evaporation to dryness. *4-4′-Glyoxalinylmethyl-2-mercaptoglyoxaline thiocyanate* (2·6 g., 42%) was obtained and was recrystallised from water forming brown needles, m. p. 207° (Found: C, 40·2; H, 3·9. $C_7H_8N_4S,CHNS$ requires C, 40·2; H, 3·8%). The free *base* separated when the thiocyanate (0·5 g.) was dissolved in a little hot water and N-sodium hydroxide (2·1 ml.) was added; recrystallised from water it formed pale brown needles, m. p. 251° (Found: C, 47·6; H, 4·0; N, 30·7; S, 17·6. $C_7H_8N_4S$ requires C, 46·7; H, 4·4; N, 31·1; S, 17·8%).

4-3′-Guanidinopropyl-2-mercaptoglyoxaline.—L-Arginine monohydrochloride (10 g.) was esterified by use of ethanol (300 ml.) saturated with hydrogen chloride. The reduction was carried out with sodium amalgam (300 g.) in the presence of potassium thiocyanate (5 g.). The solution so obtained was heated on the water-bath for 1 hour, adjusted to pH 8 with ammonia solution, and evaporated to dryness under reduced pressure. The product was then extracted with ethanol and isolated as the hydrochloride; recrystallised from water, *4-3′-guanidinopropyl-2-mercaptoglyoxaline monohydrochloride* (4·0 g., 29·5%), m. p. 245°, was obtained (Found: C, 36·0; H, 5·8; N, 31·6; S, 13·0. $C_7H_{13}N_5S,HCl$ requires C, 35·7; H, 5·9; N, 29·7; S, 13·6%). The free *base monohydrate*, m. p. 158°, was obtained by treating an aqueous solution of the hydrochloride with an equivalent amount of N-sodium hydroxide (Found: C, 38·5; H, 6·9. $C_7H_{13}N_5S,H_2O$ requires C, 38·7; H, 6·9%).

4-Hydroxymethyl-2-mercaptoglyoxaline.—DL-Serine (5 g.) was converted into its methyl ester hydrochloride by Fischer's method (*Ber.*, 1905, **38**, 4193). The crude product was reduced in the presence of potassium thiocyanate (5 g.) with sodium amalgam (2·3%, 300 g.). The resulting solution was concentrated under reduced pressure to 40 ml., filtered, and then heated for 30 minutes on the steam-bath. Solid sodium hydrogen carbonate was added to bring the pH to 7·5, and then after being acidified with dilute acetic acid, the solution was boiled with charcoal and filtered. The product was then worked up in the same way as described for 2-mercaptoglyoxaline; it had m. p. 206° (1·1 g., 18%) (Found: C, 37·3; H, 4·7. $C_4H_6ON_2S$ requires C, 36·9; H, 4·6%).

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ROYAL FREE HOSPITAL SCHOOL OF MEDICINE,
8 HUNTER STREET, BRUNSWICK SQUARE, LONDON, W.C.1. [*Received, July 28th*, 1951.]

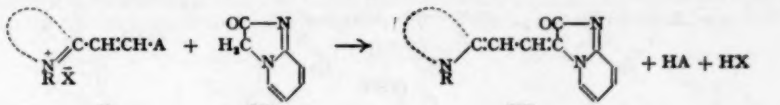
672. *The Abnormalities of Dyes Derived from* 3 : 7a-*Diazaindan-2-one.**

By Edward B. Knott.

3 : 7*a*-Diazaindan-2-one (II) has been employed in condensations to yield dimethin*mero*cyanines (III), solutions of which show a hypsochromic absorption shift on increasing the solvent polarity. These dyes are reactive towards cyclic keto-methylene compounds, yielding oxonols. In the formation of these dimethin*mero*cyanines from the diazaindanone and 2-substituted vinyl derivatives (I) of cyclic ammonium salts the formation of bis-(3 : 7*a*-diaza-1-indan-2-one)methinoxonol (IV) is observed when the diazaindanone is used in excess. The reason for the strongly dipolar nature of the dyes (III) is discussed, together with the possible mechanism of the reactions.

Dimethin*mero*cyanines, which were discovered by Kendall (B.P. 428,222; 428,360) and independently by Brooker and his collaborators (cf. Brooker, Keyes, Sprague, Van Dyke, Van Lare, Van Zandt, and White, *J. Amer. Chem. Soc.*, in the press) may be obtained by the condensation of a 2-substituted vinyl derivative of a cyclic quaternary ammonium salt (I) with a keto-methylene compound, in the presence of a base. The group A is usually an anilino-, acetanilido-, or alkylthio-residue. A variety of keto-methylene compounds has been employed in this condensation but 3 : 7*a*-diazaindan-2-one * (II) which gives dimethin*mero*cyanines of type (III) has not hitherto been used.† Various dyes have now been obtained from this substance, and their properties are of interest.

For these condensations the hydrohalide of (II) (Reindel, *Ber.*, 1924, **57**, 1381) was employed as it is more conveniently handled than the less stable base or sodium salt (see also Chichibabin, *ibid.*, p. 2072; Reindel and Rausch, *Ber.*, 1925, **58**, 393). It was noteworthy that even when



an excess of triethylamine was used to bind the acid the dyes were always obtained as the hydrohalides. The dye bases differ from known dyes of this class in possessing much greater water solubility, particularly on heating. They are also quite insoluble in non-polar solvents and exceedingly easily soluble in polar organic solvents, the dyes thus behaving as strongly polar molecules.

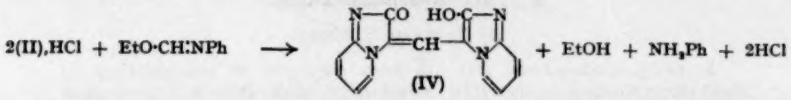
In a condensation of 2-2′-acetanilidovinylbenzoxazole ethiodide with the hydrochloride of (II) in alcoholic triethylamine, an excess of the hydrochloride was inadvertently used and, contrary to experience in a previous experiment using molar quantities of reactants, a dye crystallized during the refluxing, the normal dye being obtained from the filtrate. The alcohol-insoluble dye was very soluble in aqueous sodium carbonate or ammonia and was precipitated by acid, thus possessing the reverse characteristics of the normal dimethin*mero*cyanine. It proved to be the oxonol, bis-1-(3 : 7*a*-diazaindan-2-one)methinoxonol ‡ (IV), as shown by its analysis and preparation from (II) and ethyl*iso*formanilide. Acidification of the hot, aqueous

* This compound (II) was originally named pyrimidazolone (Reindel, *Ber.*, 1924, **57**, 1381). Allen and van Allan (*J. Org. Chem.*, 1948, **13**, 599) pointed out, however, that the name pyrimidazole has been applied to several ring systems and renamed the compound 3*a*-azaindol-2-one. Dr. Allen suggested (privately) that a more satisfactory name would be 1 : 3*a*-diazaindan-2-one in which the parent hydrocarbon is taken as the basis. This is not completely satisfactory since pyrimidazolone is not derived from indane but from the 7*aH*-isomer. The Editor has suggested 3 : 7*a*-diazaindan-2-one as the name which allows no ambiguity, in which case the presence of the 7*a*-nitrogen atom shows that there has been a shift of hydrogen from the 3-position of indane to the 7*a*-position. It will be noted that the numbering now starts from the methylene carbon and not from the methin carbon as in the name suggested by Dr. Allen.

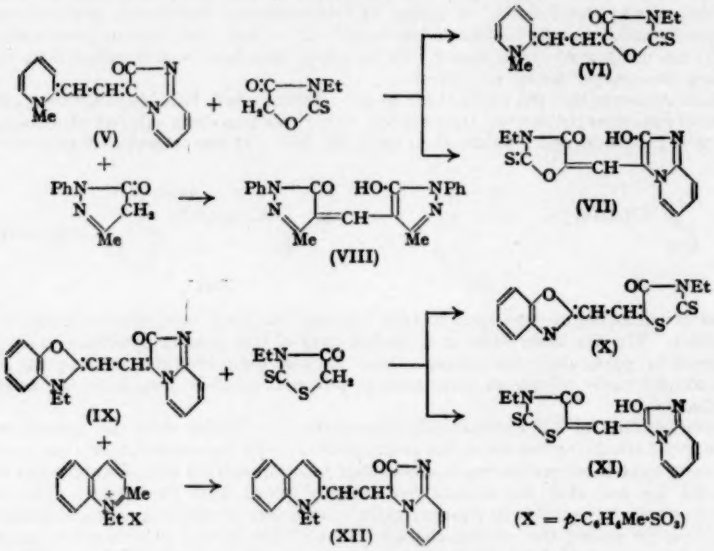
† Since this paper was written van Dormael (*Bull. Soc. chim.*, 1949, **58**, 167) has published similar condensations with this nucleus.

‡ For the oxonol nomenclature, see Hamer and Winton, *J.*, 1949, 1126.

alkaline solution of the oxonol with acetic acid gave the crystalline dihydrate but, when an excess of concentrated hydrochloric acid was used for acidification, the hydrochloride dihydrate obtained which was readily hydrolysed by water to the dihydrate.

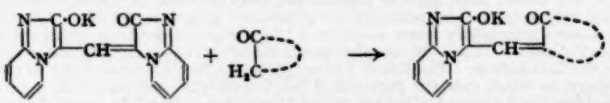


The yield of the oxonol was increased considerably when two mols. of the salt of (II) were employed for one of the quaternary salt (I). The same product was obtained irrespective of the nature of (I), although the yields varied from case to case, being particularly low when the dimethin*mero*cyanine formed a sparingly soluble hydrohalide which was precipitated from the alcoholic solution during refluxing. This fact seemed to indicate that the oxonol was formed by reaction of the second mol. of (II) with the dimethin*mero*cyanine. 2-Anilinovinyl derivatives (I; A = NHPh) of the quaternary salt gave a higher yield of oxonol than did the 2-acetanilidovinyl analogues (I; A = NPhAc). The probability that the oxonol was formed from the normal dyes was heightened by the fact that these latter are attacked not only by (II) to give (IV), but also by other compounds containing a reactive methylene or methyl group, even in the absence of a base, to give unsymmetrical oxonols, dimethin*mero*cyanines, and in one case a symmetrical oxonol. These reactions are typified by the following:



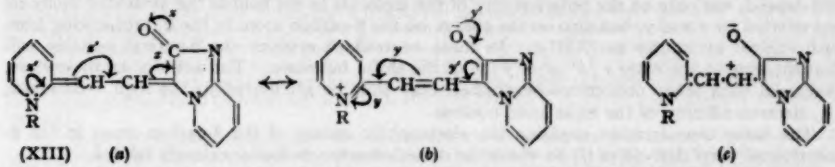
The yields of the oxonols (VII) and (XI) were higher than those of the dimethin*mero*cyanines.

The alcohol-soluble potassium salt of the oxonol (IV) is also reactive, yielding unsymmetrical oxonols on treatment with reactive keto-methylene compounds:



*The Dipolar Nature of the Dimethin*mero*cyanines*.—The abnormal behaviour of the dyes derived from (II) shows this nucleus to differ considerably from the normal type of cyclic keto-methylene compound. The behaviour as strongly polar molecules of the dimethin*mero*cyanines (III) indicates that there is a strong electron attraction by the nucleus from the rest of the

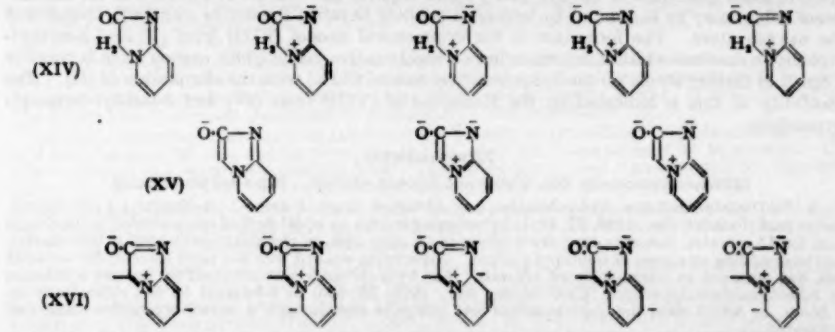
molecule, *i.e.*, the polar, extreme structure (*e.g.*, XIII*b*) in these dyes appears to be of greater significance than usual.



(XIII) (*a*) (*b*) (*c*)

This strong polarity appears in hypsochromic shifts when the polarity of the solvents is increased. This is the reverse of the usual bathochromic shifts shown by non-ionic dyes under such influences. The theoretical explanation of such a reversal was given by Förster (*Z. Elektrochem.*, 1939, **45**, 572) (see also Brooker *et al.*, *J. Amer. Chem. Soc.*, in the press; Knott, *J.*, in the press). It occurs in those dyes in which the energy level of the dipolar extreme structure (*e.g.*, XIII*b*) is of the same order as, or lower than, the level of the classical structure (*e.g.*, XIV*a*). Increasing solvent polarity then favours still more the dipolar structure, causing an increase in the non-degeneracy of the resonance system (*e.g.*, XIII*a* ⟷ XIII*b*), with a resultant hypsochromic shift.

If one considers the two extreme structures of the dye (XIII*a*, *b*) it is apparent that the pyridinium ion which constitutes the left-hand side of the molecule in (*b*) will be more stable than the dihydropyridine moiety in (*a*), since in the former, full Kekulé resonance is possible. However such a consideration applies in the case of any *mero*cyanine; consequently the behaviour of (XIII) as a strong dipole indicates that the energy of the right-hand moiety of (*a*), on acquisition of an electron to give the reduced form as in (*b*), does not increase to the same extent as it does in other cases. It is, of course, feasible that the energy of the nucleus actually decreases on reduction. The higher $+M$ effect of this nucleus, compared with others, may be explained by consideration of the number of contributing structures in the net-uncharged and net-negatively charged form.* If structures involving formal bonds are omitted then the net-uncharged form is stabilized by five important contributing structures, (XIV). On the other hand the net-negatively



(XIV) (XV) (XVI)

charged nucleus is stabilized only by three structures of this type (XV). There is, however, a further set of five stabilizing structures (XVI) which can contribute only to the net-negatively charged rings. The contributions by structures (XVI) may be of sufficient importance to account for the behaviour of the nucleus. Even if the energy of the net-negatively charged form is not greatly different from the energy of the net-uncharged form of the nucleus it may be sufficient, in conjunction with the increased stabilization of the left hand side of the molecule (XIII*b*), to increase the polarity relative to analogous dyes containing other ketonic nuclei.

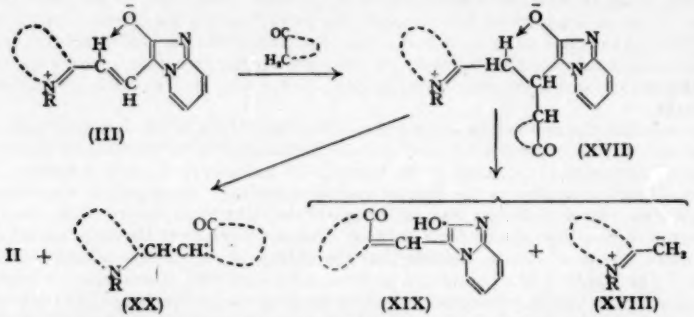
*The Mechanism of Oxonol Formation from the Dimethin*mero*cyanines.*—Although the isolation of intermediate products has not been possible it seems reasonable to assume that the formation of oxonols from these dimethin*mero*cyanines depends primarily on the attack by the nucleophilic carbon atom of the methylene group on the electrophilic β-carbon atom of the chain of the dye. If the two extreme structures (*a*) and (*b*) of the dye (XIII) are considered, then the

* For some of these considerations the author is indebted to Dr. L. G. S. Brooker.

electromeric processes involved in (*a*) are denoted by x and in (*b*) by y. The mesomeric processes in each case are represented by x'–x and y–y'. The electrophilic strength of the β-carbon atom will depend, not only on the polarisability of the molecule in the field of the attacking molecule represented by x and y, but also on the charge on the β-carbon atom in the hybrid arising from such excited structures as (XIIIc). In these neutralized systems the β-carbon activity will thus increase as the ratio $x : x'$ or of $y : y'$ of the shifts increases. The activity of these dyes, compared with other dimethin*mero*cyanines, may thus be attributed to the high $+M$ effect, *i.e.*, electron affinity, of the right hand nucleus.

The same consideration explains the electrophilic nature of the β-carbon atom in the β-substituted vinyl derivative (I) to which the dimethin*mero*cyanines are closely related.

The attack on the dye (III) by a keto-methylene compound is then pictured as follows. The unstable intermediate (XVII) expels either the methylene base (XVIII) to give the oxonol (XIX), or (II) to give the second dimethin*mero*cyanine (XX). The expulsion of (XVIII) requires no



transfer of proton and this may be the reason why the oxonol is the main product. The formation of small quantities of the dye (XX), which requires the transfer of a proton to the diazaindenol anion, may be facilitated by hydrogen bonding between the active α-chain-hydrogen and the oxygen atom. The formation of the symmetrical oxonol (VIII) from (V) and 3-methyl-1-phenylpyrazolone which is known to have a highly active, nucleophilic carbon atom is possibly a result of further attack on the unsymmetrical oxonol (XIX) with the elimination of (II). The feasibility of this is indicated by the formation of (VIII) from (IV) and 3-methyl-1-phenyl-pyrazolone.

Experimental.

Microanalyses are by Drs. Weiler and Strauss, Oxford. M.p.s are uncorrected.

3 : 7a-Diazaindan-2-one hydrochloride was obtained from 2-imino-1 : 2-dihydro-1-pyridylacetic acetic acid (Reindel, *Ber.*, 1924, **57**, 1381) by refluxing it with an equal part of concentrated hydrochloric acid for 15 minutes, concentrating the mixture in an open dish on the steam-bath until it was viscous, and then adding an excess of *iso*propyl alcohol. After being washed with the same solvent, the required salt was obtained as cream-coloured crystals. The hydrobromide was obtained by heating a solution of 2-bromoacetamidopyridine (Chichibabin, *ibid.*, 1925, **58**, 393) in *n*-butanol on the steam-bath for 4 hours, by which time the quaternisation was complete and the salt, a brown crystalline mass, had separated.

[3 : 7a-*Diaza*-1-*indan*-2-*one*][1-*ethyl*-2-*quinoline*]*dimethin*merocyanine (XII).—2-2′-Acetanilidovinyl-quinoline ethiodide (4·44 g., 0·01 mol.) was dissolved in hot ethanol (50 c.c.) and a solution of 3 : 7a-diazaindan-2-one hydrobromide (2·15 g., 0·01 mol.) in ethanol (50 c.c.) was added, followed by triethylamine (2·8 c.c., 0·02 mol.). After 2 minutes' boiling the dye *hydriodide*, m. p. 300°, separated as golden crystals. It was purified by being boiled several times with ethanol (Found : N, 9·5; I, 27·5. $C_{30}H_{28}ON_3I$ requires N, 9·5; I, 28·85%). The *base* was obtained by dissolving the salt in alcoholic triethylamine and precipitating with water. After drying in air it was dissolved in ethanol, and ether was run into the hot solution until crystallisation commenced. The dye, m. p. 266°, collected after the solution had cooled, formed purple needles with a green reflex (Found : N, 13·6. $C_{30}H_{27}ON_3$ requires N, 13·3%), $\lambda_{max.}$ 562 (in methanol), 543 mμ. (in aqueous methanol).

[3 : 7a-*Diaza*-1-*indan*-2-*one*][3-*ethyl*-2-*benzoxazole*]*dimethin*merocyanine (IX).—2-2′-Acetanilidovinyl-benzoxazole ethiodide (4·34 g.), 3 : 7a-diazaindan-2-one hydrobromide (2·15 g.), triethylamine (2·8 c.c.), and ethanol (25 c.c.) were refluxed together for 30 minutes. Triethylamine and alcohol were partly removed by distillation and, on cooling, the *hydrobromide* (4 g.) crystallised. It formed red needles, m. p. 202°, from ethanol (Found : N, 10·5; Br, 20·65. $C_{18}H_{16}O_2N_3Br$ requires N, 10·9; Br, 20·7%). The *base* was obtained as yellow flakes on addition of aqueous sodium carbonate to the warm aqueous

solution of the salt, followed by chilling. It is very difficult to filter. It formed orange crystals, m. p. 269°, from water (Found : N, 13·6. $C_{18}H_{15}O_2N_3$ requires N, 13·8%), $\lambda_{max.}$ 502 mμ. (in methanol).

[3 : 7a-*Diaza*-1-*indan*-2-*one*][3-*ethyl*-2-*benzthiazole*]*dimethin*merocyanine, was obtained as a very insoluble salt on refluxing for 30 minutes a mixture of the diazaindanone hydrobromide (2·15 g.), 2-2′-acetanilidovinylbenzthiazole ethiodide (4·5 g.), triethylamine (2·8 c.c.), and ethanol (25 c.c.). The *base* was released as for the previous dye, and obtained as red needles or small green crystals, m. p. 271°, from ethanol–ether (Found : N, 12·6; S, 9·95. $C_{18}H_{15}ON_3S$ requires N, 13·1; S, 10·0%), $\lambda_{max.}$ 532 mμ. (in methanol). The *hydrobromide* was obtained as red needles, m. p. 309°, by dissolving the base in ethanol and adding a solution of hydrobromic acid in acetic acid (Found : N, 10·4. $C_{18}H_{16}ON_3Br$ requires N, 10·45%).

[3 : 7a-*Diaza*-1-*indan*-2-*one*][3-*ethyl*-2-*thiazolidine*]*dimethin*merocyanine.—A mixture of 2-2′-acetanilidovinylthiazoline ethiodide (4 g.), the diazaindanone hydrobromide (2·15 g.), triethylamine (2·8 c.c.), and ethanol (25 c.c.) was refluxed for 30 minutes and concentrated to half volume. On chilling, a mixture (4 g.) of purple needles and orange rosettes was obtained. The base was extremely soluble in water and was not isolated. The *hydrobromide* was obtained as orange rosettes, m. p. 236°, by dissolving the crude product in hot alcohol and adding a solution of hydrobromic acid in acetic acid (Found : N, 11·4; Br, 22·0. $C_{14}H_{16}ON_3SBr$ requires N, 11·85; Br, 22·6%), $\lambda_{max.}$ 479 mμ. (in methanol).

[3 : 7a-*Diaza*-1-*indan*-2-*one*][1-*methyl*-2-*pyridine*]*dimethin*merocyanine (V).—2-2′-Anilinovinylpyridine methiodide (3·5 g.) was heated under reflux for 30 minutes with acetic anhydride (10 c.c.), then chilled, and the acetanilidovinyl derivative precipitated with ether. The oil was washed with ether and refluxed with 3 : 7a-diazaindan-2-one hydrobromide (2·15 g.), triethylamine (2·8 c.c.), and ethanol (25 c.c.) for 30 minutes. The *hydrobromide* commenced to crystallise after a few minutes. It (2·7 g.) formed a purple powder, m.p. 268°, from methanol (Found : N, 12·5. $C_{15}H_{14}ON_3Br$ requires N, 12·65%). The *base* was obtained as purple needles, m. p. 261°, from water. It contained water of crystallisation, removed at 110° (Found : N, 16·4. $C_{15}H_{13}ON_3$ requires N, 16·7%), $\lambda_{max.}$ 525 (in methanol), 464 mμ. (in water).

[3 : 7a-*Diaza*-1-*indan*-2-*one*][1-*ethyl*-4-*pyridine*]*dimethin*merocyanine was obtained similarly from 4-2′-anilinovinylpyridine ethiodide (3·7 g.). The *hydriodide* (2 g.) formed fine purple hairs, m. p. 267°, from methanol (Found : N, 10·1. $C_{18}H_{16}ON_3I$ requires N, 10·7%), and the *base dihydrate*, red needles from water (Found : N, 14·1. $C_{18}H_{15}ON_3,2H_2O$ requires N, 13·95%), $\lambda_{max.}$ 542 mμ. (in methanol).

Bis-(3 : 7a-*diaza*-1-*indan*-2-*one*)*methinoxonol* (IV).—(*a*) 3 : 7a-Diazaindan-2-one hydrochloride (3·4 g., 0·02 mol.), ethanol (200 c.c.), and triethylamine (2·8 c.c.) were heated to effect dissolution, and ethyl *iso*formanilide (1·5 g., 0·01 mol.) added. A brick-red solid (2·5 g.), m. p. 300°, separated. For purification this *oxonol* was boiled several times with ethanol (Found : C, 64·6; H, 3·5; N, 20·1. $C_{15}H_{10}O_2N_4$ requires C, 64·75; H, 3·6; N, 20·5%). After its dissolution in boiling aqueous ammonia and then neutralisation with acetic acid, rose-coloured needles of the *dihydrate* separated on cooling (Found : C, 57·1; H, 4·5; N, 17·5. $C_{15}H_{10}O_2N_4,2H_2O$ requires C, 57·35; H, 4·5; N, 17·65%). The addition of excess of concentrated hydrochloric acid to the ammoniacal solution of the base gave orange needles of the *hydrochloride dihydrate* (Found : Cl, 10·1. $C_{15}H_{10}O_2N_4,HCl,2H_2O$ requires Cl, 10·15%). Further typical experiments are as follows.

(*b*) 2-2′-Acetanilidovinylbenzoxazole ethiodide (8·7 g., 0·01 mol.), the diazaindanone hydrochloride (4·3 g., 0·0125 mol.), ethanol (20 c.c.), and triethylamine (2·8 c.c., 0·02 mol.) were refluxed for 30 minutes. The oxonol (2·2 g.) was obtained as a brick-red crystalline powder (Found : C, 64·4; H, 3·75; N, 20·2%). The filtrate gave the normal dimethin*mero*cyanine salt on concentration.

(*c*) 2-2′-Anilinovinylthiazoline methiodide (3·6 g., 0·01 mol.), the diazaindanone hydrochloride (3·4 g., 0·02 mol.), ethanol (20 c.c.), and triethylamine (2·8 c.c., 0·02 mol.) were refluxed for 10 minutes. The whole solidified to a brick-red crystalline mass. The oxonol (3·9 g.) was converted into the dihydrate (Found : C, 56·95; H, 4·55; N, 18·4%) and hydrochloride dihydrate (Found : Cl, 9·85%).

(*d*) The compound (IX) (3·41 g., 0·01 mol.), 3 : 7a-diazaindan-2-one hydrochloride (1·7 g., 0·01 mol.) triethylamine (1·4 c.c., 0·01 mol.) (may be omitted), and ethanol (20 c.c.) were refluxed for 1 hour. The oxonol (2·4 g., 86·5%) separated during this time (Found : N, 20·3%).

*Reactions of Dimethin*merocyanines.—(*a*) The cyanine (V) (2·5 g.), 3-ethyl-4-keto-2-thio-oxazolidine (1·45 g.), and ethanol (15 c.c.) were refluxed for 3 hours. The solid which separated was boiled with aqueous sodium carbonate, leaving purple needles undissolved. The latter (0·2 g.) formed metallic spears, m. p. 254° from pyridine (Found : C, 59·8; H, 5·5; N, 10·4. Calc. for $C_{18}H_{14}O_2N_2S$: C, 59·6; H, 5·35; N, 10·7%). It is [3-ethyl-4-keto-2-thio-5-oxazolidine][2-methyl-1-pyridine]dimethin*mero*cyanine (VI). The filtrate from the reaction mixture gave an orange precipitate on addition of water ; this was obtained as orange-brown crystals (1·9 g.), m. p. 292° (decomp.), from aqueous sodium carbonate and is [3 : 7a-*diaza*-1-*indan*-2-*one*][3-*ethyl*-4-*keto*-2-*thio*-5-*oxazolidine*]*methinoxonol* (VII) (Found : N, 14·4; S, 8·5. $C_{18}H_{11}O_3N_3S$ requires N, 14·4; S, 8·7%).

(*b*) The base (IX) (3·05 g.), treated similarly, gave the analogous [3-ethyl-2-benzoxazole][3-ethyl-4-keto-2-thio-5-oxazolidine]dimethin*mero*cyanine (0·95 g.) (Found : C, 61·2; H, 5·05; N, 8·25; S, 10·1. Calc. for $C_{17}H_{14}O_3N_2S$: C, 60·8; H, 5·05; N, 8·35; S, 9·75%). The filtrate gave 2·1 g. of the oxonol formed as recorded in (*a*) (Found : C, 54·25; H, 3·85%).

(*c*) The base (IX) (3·05 g., 0·01 mol.), 3-ethylrhodanine (1·6 g., 0·01 mol.), and ethanol (20 c.c.) were refluxed for 2 hours. After 10 minutes, crystals commenced to form. After cooling, the solid (2·4 g.), which was a mixture, was collected, and the oxonol removed by boiling 2N-sodium carbonate. The residue (0·5 g.) formed yellow needles, m. p. 230°, from ethanol (Found : C, 57·5; H, 4·75; N, 10·0; S, 19·05. Calc. for $C_{16}H_{14}O_2N_2S_2$: C, 57·55; H, 4·7; N, 9·65; S, 19·3%). It is [3-ethyl-2-benzoxazole][3-ethyl-4-keto-2-thio-5-thiazolidine]dimethin*mero*cyanine (X). The carbonate extract, together with the dye precipitated by water from the reaction mixture filtrate, gave 2·5 g. of [3 : 7a-*diaza*-1-

indan-2-one][*3-ethyl-4-keto-2-thio-5-thiazolidine*]*methinoxonol* (XI), which formed a steel-grey crystalline powder, m. p. 300°, from formamide (Found: C, 51·15; H, 3·95; N, 13·5; S, 20·95. $C_{15}H_{11}O_3N_3S_3$ requires C, 51·1; H, 3·6; N, 13·8; S, 21·0%).

(*d*) The oxonol (IV) (2·5 g., 0·01 mol.), 3-methyl-1-phenylpyrazolone (1·74 g., 0·01 mol.), and ethanol (20 c.c.) were refluxed for 1½ hours. On dilution with water a yellow precipitate was given which on recrystallisation from ethanol formed yellow needles (1·1 g.), m. p. 175° alone or mixed with an authentic specimen of (VIII) (Found: N, 15·3. Calc. for $C_{11}H_{10}O_3N_4$: N, 15·6%).

(*e*) The base (IX) (3·05 g., 0·01 mol.), quinaldine ethotoluene-*p*-sulphonate (3·43 g., 0·01 mol.), and ethanol (25 c.c.) were refluxed together for 2 hours. The purple solution was then poured into water and the dimethin*mero*cyanine (XII) collected; it formed purple needles (1·1 g., 35%) with a green reflex, m. p. 265°, identical with the product obtained earlier (Found: N, 13·4%).

Reactions of the Oxonol (IV).—(*a*) The oxonol (1·4 g., 0·005 mol.) and 3-ethyl-4-keto-2-thio-oxazolidine (0·75 g., 0·005 mol.) were suspended in a solution of potassium hydroxide (0·6 g.) in alcohol (30 c.c.) and refluxed for 1 hour. The resultant clear solution was acidified with dilute hydrochloric acid, and the precipitate recrystallised from aqueous sodium carbonate. It formed orange-brown crystals (1·05 g., 77·5%), m. p. 292° (decomp.), identical with (VII) obtained earlier (Found: S, 9·4%).

(*b*) The oxonol (1·4 g.), 3-methyl-1-phenylpyrazolone (0·87 g., 0·005 mol.), and a solution of potassium hydroxide (0·4 g.) in alcohol (30 c.c.) were refluxed for 1 hour. The clear, hot solution was acidified, and the orange crystals (1·3 g.) were collected on cooling. They were repeatedly extracted with *iso*propyl ether, to give 0·45 g. (50%) of the ether-soluble oxonol (VIII), m. p. 176° alone or mixed with an authentic specimen (Found: N, 15·4%).

RESEARCH LABORATORIES,
KODAK LIMITED, WEALDSTONE, MIDDLESEX.

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673. *The Colour of Organic Compounds. Part V.* Thermochromic Spirans.*

By EDWARD B. KNOTT.

The factors affecting the thermochromic behaviour of certain spirans containing one or more pyran residues have been analysed. It is shown that, whereas the ease of intramolecular ionization resulting in dye formation increases with an increasing $-M$ effect of the heterocyclic *spiro*-component (cf. Wizinger and Wenning, *Helv. Chim. Acta*, 1940, **23**, 247), it may be affected in either direction by changes in the $+M$ effect of the ketonic fragment resulting from the ring-opening and is largely independent of the degree of degeneracy of the resonance system responsible for the colour of the dye. The inhibitory effect of the introduction of substituents into certain positions of the pyran rings is explained on the basis of steric hindrance to planarity of the dye molecules. Certain colour phenomena associated with Wizinger's dyes are explained on the basis of their strongly dipolar nature.

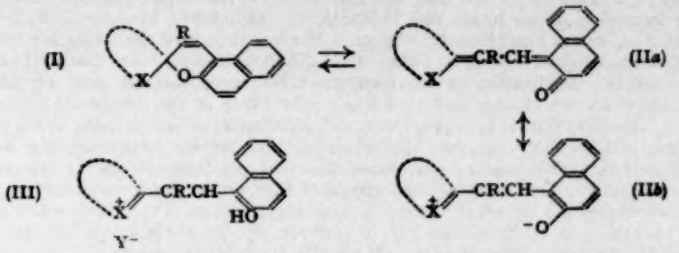
THE thermochromic behaviour of certain colourless *spiro*bispyrans is well known (for references see Mustafa, *Chem. Reviews*, 1948, **43**, 509), and the explanation of the formation of colour is now generally accepted as being due to an intramolecular ionization proceeding according to (I; X = O) ⟶ (II; X = O),† the broken line denoting the atoms necessary to complete the heterocyclic ring. Dickenson and Heilbron (*J.*, 1927, 1699) have shown that the property of thermochromicity is only exhibited by those spirans (I; X = O) which contain at least one naphthopyran ring and a free 3-position (I; X = O, R = H). The same process also appears to be involved in related spirans in which X = NR (Wizinger and Wenning, *Helv. Chim. Acta*, 1940, **23**, 247).

* Part IV, *J. Soc. Dyers and Colourists*, 1951, in the press.

† Hukins and Le Fèvre (*J.*, 1949, 2088) and Bergmann, Weizmann, and Fischer (*J. Amer. Chem. Soc.*, 1950, **72**, 5009) have shown that the expected increase in dipole moment of *spiro*bispyrans when heated to give colour is not measurable. These authors suggest, therefore, that the least unacceptable hypothesis for the structure of the coloured molecule is the quinone (*e.g.*, IIa). Bergmann *et al.* also refer to the stable dye [1-methyl-2-quinoline][1 : 2-dihydro-2-ketonaphthalene]dimethin*mero*cyanine as *N*-methylquinolino-β-naphthopyrylospiran. They appear thus to be unaware of three fundamental principles involved: (*a*) That in the spiran there is no π-electron orbital overlap between the two halves at right angles to each other. Consequently atomic movement towards planarity is required in order that (IIa) and (IIb) can contribute. (*b*) That in such a case there must be a resonance system with (IIa) and (IIb) as extreme structures. (*c*) That for deep and intense colour near-planarity of the molecule is required with not greatly dissimilar contributions by both extreme structures.

The experimental results of the above authors can thus best be explained on the basis of the relatively small percentage of spiran molecules excited to dye molecules at any particular moment at the relatively low temperatures employed (60° and 90° respectively).

Wizinger and Wenning concluded that the ease of ionization would increase as the electron donating properties ($-M$ effect) of the atom or group X increased. Thus they found that compounds where X = NR are more thermochromic than those in which X = O and that in



the extreme case the coloured, " ionic " form was stable at room temperature. They called the latter dyes, spirains, but in this paper they will be given the more usual name of dimethin-*mero*cyanines. They were obtained by these authors by employing 1-formyl-2-naphthol in the well-known reaction between aldehydes and cyclic quaternary ammonium salts carrying a reactive methyl group (König, *J. pr. Chem.*, 1912, **86**, 166; Barbier, *Bull. Soc. chim.*, 1920, **27**, 429). The resultant stable 1-(2-hydroxy-1-naphthyl)vinyl derivative of the quaternary salt (III; X = NR) gave (II) on treatment with a base. In two cases this treatment resulted in spontaneous isomerisation to the spiran (I; X = NR), namely, in those dyes containing the 1 : 3 : 3-trimethylindoline and 9 : 10-dihydro-10-methylacridine nuclei. No such isomerization occurred, however, in the dyes containing the 3-ethylbenzothiazoline, 3-ethylbenzoselenazoline, 1 : 2-dihydro-1-methylquinoline, or 1 : 2-dihydro-1 : 4 : 6-triphenylpyridine nuclei. The increased ease of ionization of these spirans (I; X = NR), compared with (I; X = O), was demonstrated by the development of colour even in cold solutions in polar solvents and by the thermochromic behaviour of the benzopyran (as I; X = NR, less one benzene ring).

We shall now consider the electronic processes which occur on ionization in order to determine those factors which will favour or inhibit such ionization.

The Electronic Processes and Energy Considerations affecting Ionization.—As with any reaction, the ease of intramolecular ionization of these spirans would be expected to depend on the relative energy levels of the ground states of the dye and of the spiran. If such extramolecular factors as temperature and solvent polarity (which will be of importance in determining the spiran–dye equilibrium) are excluded, it may be argued that the stability of the dye relative to that of the spiran will depend on the free energy associated with (*a*) the $-M$ effect of the heterocyclic component containing X, (*b*) the $+M$ effect of the carbocyclic (ketonic) residue, and (*c*) the resultant interaction of these two effects, *i.e.*, the resonance (IIa ⟶ IIb) responsible for visible absorption. The effect, on ionization, of changes in these three factors resulting from structural alterations will now be examined.

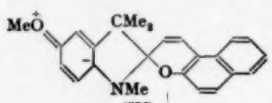
The factor (*a*). This factor, applied to the spiran, is that given by Wizinger and Wenning (*loc. cit.*), who refer to it as a change in the " Positivierung " of the carbon atom of the spiran molecule common to both *spiro*-components. They give no fundamental theoretical explanation of the effect, which is believed to be as follows. The $-M$ effect of the heterocyclic system is related to the free energy involved in the process (IIa ⟶ IIb) and will increase with increasing free-energy change; it involves the ionization potential of the atom X and the simultaneous changes in the resonance energy of the nucleus itself. Any structural changes in the heterocyclic system which alter the strength of its $-M$ effect in the direction of the *spiro*-carbon atom cannot affect the ground state level of the spiran by virtue of such a change in $-M$ effect, since it cannot operate. On the other hand, such a change will affect the resonance energy, and hence the ground-state level, of the dye in which the $-M$ effect is operative. As the latter increases, so will this level fall, with a resultant increase in ease of ionization of the corresponding spiran. This may be pictured as an increased stabilization of the extreme structure (IIb) of the dye and of all excited structures containing the quaternary-nitrogen heterocyclic system.

The correctness of this interpretation was shown by Wizinger and Wenning's experimental evidence (*loc. cit.*). In the first place, the greater ease of ionization of the spirans where X = NR, compared with those where X = O, is a manifestation of the greater $-M$ effect of

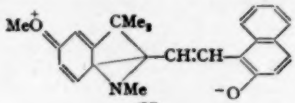
the NR group. Those nuclei, *i.e.*, 1 : 3 : 3-trimethylindoline and 9 : 10-dihydro-10-methylacridine, which form spirans must clearly on this hypothesis possess weaker $-M$ effects than the other nuclei. Brooker (*Rev. Mod. Physics*, 1942, **14**, 275; Burk and Grummit, "Frontiers in Chemistry," Interscience Publ. Inc., Vol. III, Chap. IV) has indeed shown, by his absorption deviation method (see also Knott and Williams, *J.*, 1951, 1586), that the 1 : 3 : 3-trimethylindoline nucleus exerts a significantly weaker $-M$ effect than does the 3-ethylbenzothiazoline, 3-ethylbenzoselenazoline, 1-ethyl-1 : 2(or 1 : 4)-dihydroquinoline, or 1-ethyl-1 : 2-dihydropyridine nucleus. Application of the qualitative resonance method used by Brooker to interpret his series would also lead to a weak $-M$ effect of the dihydro-10-methylacridine nucleus (cf. Brooker, White, Sprague, Dent, and van Zandt, *Chem. Reviews*, 1947, **41**, 325).

Wizinger and Wenning (*loc. cit.*) also observed that spirans containing the 5-methoxy-1 : 3 : 3-trimethylindoline nucleus were more chromotropic than the parent spirans without the methoxy-group. This is readily understood in that, whilst the introduction of this group will stabilize the spiran by contributions of such structures as (IV), it will stabilize the dye not only by analogous contributions but, in addition, by the participation of such structures as (V), *i.e.*, by effectively increasing the $-M$ effect of the indoline nucleus.

The factor (*b*). Although an increase in the $+M$ effect of the ketonic nucleus will again stabilize the dipolar extreme structure of the dye this does not necessarily mean that a resultant increase in ease of ionization of the spiran will occur. If the free-energy change on electron



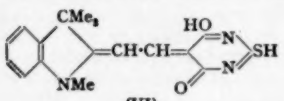
(IV)



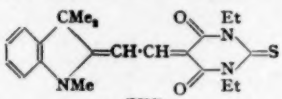
(V)

capture by this nucleus is negative, the resultant stabilization of the nucleus is felt both by the dye and also by the spiran since the latter contains this nucleus (as the pyran nucleus) in its reduced form. It is necessary, therefore, in determining the effect of changes in $+M$ effect, to analyse each case separately and it will be shown below that, depending on the nature of the structural change, an increase in $+M$ effect may stabilize either the spiran or the dye.

In the first place it can be shown, by employing the same empirical reasoning as was applied by Brooker (*loc. cit.*) to pyridine and quinoline, that the $+M$ effect of the 2-keto*cyclo*hexa-3 : 5-dienylidene residue is greater than that of the 1 : 2-dihydro-2-ketonaphthylidene residue

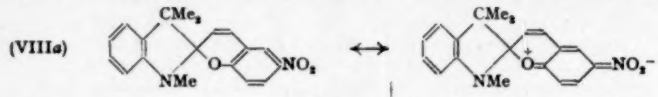


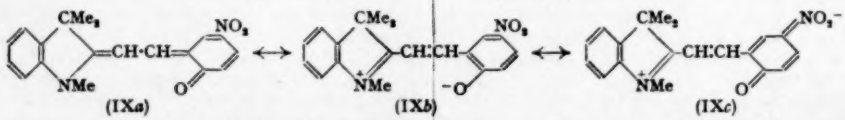
(VI)



(VII)

(this is manifested experimentally by the lower nucleophilic activity of the 2-position in the phenoxide ion compared with the 1-position in the 2-naphthoxide ion). Reasoning similar to that used by Brooker (*loc. cit.*) shows the naphthopyran (I) (the nitrogenous heterocyclic component being neglected) to be stabilized by three major contributing (Kekulé) structures,





and the dye (II*a*, *b*) (both II*a* and II*b* being assumed to be significant) by five major structures (two in II*a* and three in II*b*). The loss of the extra benzene ring reduces the number of such structures in the spiran to two and in the dye to three. On this reasoning, therefore, such a structural change would be expected to result in spiran stabilization. This is in agreement with experimental evidence (see earlier) and may be a contributory cause.

Further examples of this effect are provided by the fact that dimethin*mero*cyanines containing a heterocyclic ketonic nucleus show no tendency at all to spiran formation, even when the latter nucleus is six-membered. Thus, for example, [1 : 3 : 3-trimethyl-2-indolenine]-[5 : 6-dihydro-4-hydroxy-6-keto-2-mercapto-5-pyrimidine]dimethin*mero*cyanine (VI) Kendall B.P. 428,722; 428,360) or [1 : 3 : 3-trimethyl-2-indoline][1 : 3-diethylhexahydro-2-thio-5-pyrimid-4 : 6-dione]dimethin*mero*cyanine (VII) are quite stable at low temperatures, consistently with the much weaker $+M$ effect of the thiobarbituric acid residues compared with the dihydroketo-aromatic systems.

As a second type of structural change resulting in a change in the $+M$ effect of the ketonic nucleus, the introduction of substituents in the ketonic nucleus was studied. The nitro-group was selected for convenience and because of its strong $+M$ effect. 2-Hydroxy-3- and -5-nitrobenzaldehyde were condensed with a number of cyclic quaternary ammonium salts carrying a reactive methyl group. Stable dyes were obtained in all cases, except with trimethylindolenine methiodide which yielded 1 : 3 : 3-trimethyl-8′- and -6′-nitroindoline-2-*spiro*-2′-benzopyran (VIII*a*, *b*). The introduction of this nitro-group will stabilize the spiran by contributions by such structures as (VIII*b*).

In the dye the presence of the nitro-group will not appreciably affect the resonance energy of the non-polar extreme structure (IX*a*), but the dipolar extreme structure (IX*b*) will acquire considerable additional stabilization by important contributions of (IX*c*). It appears probable that the resonance (IX*b* ⟷ IX*c*) is more significant than (VIII*a* ⟷ VIII*b*) since, in the latter, energy of charge separation is involved. Consequently the increase in the $+M$ effect of the nucleus by the introduction of the nitro-group would be expected to favour ionization of the spiran. This is confirmed experimentally, both nitro-spirans, and particularly (VIII), being more readily ionized than the parent compound (Wizinger and Wenning, *loc. cit.*). Even in cold polar solvents, such as alcohol, intensely red solutions are obtained.

If, on the other hand, a $-M$ substituent is introduced into the ketonic nucleus a decrease in its $+M$ effect will result. This decrease however is not due to a rise in the energy of the

(X*a*) (X*b*)

dipolar extreme structure relative to that of the classical structure (X*a*), but rather to a fall in the energy of the latter structure owing to contributions of such structures as (X*b*). Since such additional resonance stabilization is not enjoyed by the corresponding spiran the introduction of this $-M$ substituent can only favour ionization. This was shown to be true by Wizinger and Wenning (*loc. cit.*) who recorded that the introduction of a methoxy-group favoured dye formation.

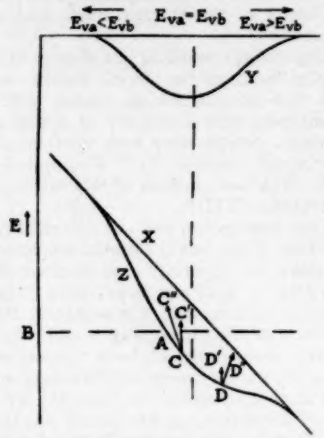
The factor (*c*). The energy associated with the resonance responsible for colour will be at a maximum at the point of accidental degeneracy, *i.e.*, when $E_{\text{IIa}} = E_{\text{IIb}}$. Loss of such degeneracy may occur in four ways, by the raising or lowering of the energy level of either extreme structure. At this point it is not known whether E_{IIa} is greater or less than E_{IIb}, but if, for the moment, it is assumed that $E_{\text{IIa}} < E_{\text{IIb}}$ then any increase in the $-M$ effect of the heterocyclic system will decrease the non-degeneracy of the resonance system until degeneracy is achieved, and any further increase in this effect will result in E_{IIa} becoming greater than E_{IIb} with a resultant increase in non-degeneracy (Förster, *Z. Elektrochem.*, 1939, **45**, 545). Although in this progression the resonance energy of the system (IIa ⟷ II*b*) rises and then falls again, this does not mean that the dye–spiran stability ratio is at a maximum at the point of degeneracy; for such changes, in general, increasingly lower the energy of the dipolar extreme structure, and hence of the hybrid relative to that of the spiran, even beyond the point of attainment of degeneracy. The degree of non-degeneracy of this system in itself is, therefore, not an essential factor which determines spiran or dye stability.

It is obvious, however, that if such a progression is assumed, the superimposition of the increasing resonance energy of the system (IIa ⟷ II*b*) will accelerate the favouring of dye formation up to the point of degeneracy, and beyond this point will decelerate the process. This may be represented by Fig. 1, in which energy is plotted against the ratio $E_{\text{IIa}} : E_{\text{IIb}}$, the vertical broken line representing the point $E_{\text{IIa}} = E_{\text{IIb}}$. The line X represents the constant decrease in E_{IIb} relative to E_{spiran} as the $-M$ effect of the heterocyclic nucleus increases. The shape of curve Y, and its position relative to the other curves, are purely artificial; this curve represents the resonance energy $E_{(\text{IIa} \longleftrightarrow \text{IIb})}$, and curve Z is the resultant of X and Y. The

point A represents the ratio $E_{IIa} : E_{IIb}$ at which dye formation, under the particular conditions chosen, does not occur. The minimum value of E_{spiran} will then always lie above the point B.

It has been pointed out above that the resonance energy of the system IIa ⟷ IIb will favour dye formation although changes in its value brought about by changes in the $+M$ and

FIG. 1.



the $-M$ effects of the two nuclei are less important. It is possible however to change its value without structural change of the nuclei and without altering their M effects. Suppose that the ground level of the dye lies either at a point C or D (on curve Z). If now a substituent is introduced into the chain, which causes overcrowding, the latter may be relieved by a twisting

FIG. 2.

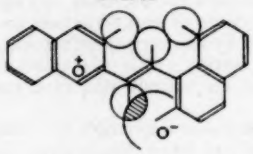


FIG. 3.

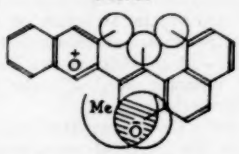


FIG. 4.

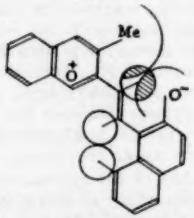
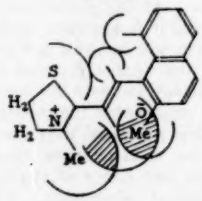


FIG. 5.

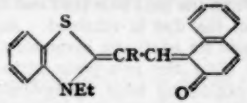


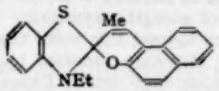
of the chain bonds which causes a loss of coplanarity of the two nuclei. The value of $E_{IIa \leftrightarrow IIb}$ will consequently fall, owing to a reduction in the overlap of the π-electron orbitals. The ground level of the dye may now be represented by points C' or D'. However, if the twisting is severe the energetic asymmetry of the dye will be affected, causing a further shift in $E_{IIa \leftrightarrow IIb}$. Unless the system IIa ⟷ IIb is near-degenerate such twisting can only cause an increase in the energetic asymmetry of the molecule (cf. Brooker *et al.*, *loc. cit.*), so that the points C'' or D'' now represent the dye ground level. The diagram shows the theoretical possibility of the introduction of an overcrowding substituent causing a stable dye to revert

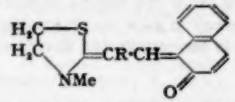
to spiran since the energy points *C'* or *C''* lie above the point *B*. It also shows that the likelihood of such an occurrence will decrease with increasing dye polarity. This explains the inhibition of thermochromotropy in *spiro*bispyrans (I; X = O) by substituents.

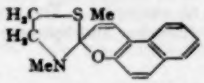
Fig. 2 shows a scale drawing of the dye obtained by the ionization of benzopyran-2-*spiro*-2'-[naphtho(2'' : 1''-2 : 3)pyran]. Although there is some overcrowding between a chain-hydrogen atom and the negatively charged oxygen atom the dye may be considered to be near-planar. The introduction of a substituent, to give 3'-methylbenzopyran-2-*spiro*-2'-[naphtho(2'' : 1''-2 : 3-pyran] (cf. I; X = O, R = Me), is known to inhibit completely its thermochromic properties. Fig. 3 represents the least overcrowded configuration of the hypothetical dye resulting from this spiran and it will be seen that the chain-methyl group will prevent the naphthyl residue from being coplanar with the rest of the molecule. On the other hand, the introduction of a methyl group to give the 3-methyl spiran is known not to inhibit ionization and, as Fig. 4 shows, the resultant dye is only slightly more overcrowded than the parent dye.

It has now also been found possible to demonstrate the effect at room temperature. Whereas the condensation of 2-methylbenzothiazole ethiodide (Wizinger and Wenning, *loc. cit.*) or 2-methylthiazoline methiodide with 1-formyl-2-naphthol, followed by treatment of the product with a base, gave the dyes (XI; R = H) and (XIII; R = H) respectively, the use of the 2-ethyl homologues led to (XII) and (XIV). Of these, (XII) is the more easily

(XI) 


(XII)

(XIII) 


(XIV)

ionized, giving red solutions in polar solvents and a purple melt. The dye (XIV) gave a yellow melt, consistently with the lighter colour usually associated with the thiazolidine nucleus. The higher stability of (XIV) is also consistent with the weaker $-M$ effect of the 2-thiazolidine nucleus, as found by Brooker (*loc. cit.*). The degree of overcrowding in (XIII; R = Me) (the same applies to XI) is shown in Fig. 5. Treatment of solutions of (XII) and (XIV) with gaseous hydrogen chloride readily gave the corresponding chlorides of type (III).

The Effect of Polar Solvents on Spiran Stability.—It has been mentioned earlier that, apart from structural considerations, the polarity of the solvent will be of importance in determining the spiran–dye equilibrium in solution. Thus Wizinger and Wenning (*loc. cit.*) reported the development of colour on addition of water to the colourless solutions of certain of these spirans in water-miscible non-polar or weakly polar solvents such as pyridine. This effect is particularly well shown by 1 : 3 : 3-trimethylindoline-2-*spiro*-2'-[naphtho(1' : 2'-5'' : 6'')pyran] (or its derivatives) which gives colourless solutions in light petroleum and intensely purple ones in *o*-chlorophenol. The favouring of dye formation or increase of solvent polarity may be directly ascribed to the hydrogen-bonding properties of aqueous or other polar solvents which, while affecting the ground-state level of the spiran but slightly, will decrease considerably more the energy levels of all dipolar structures contributing to the resonance hybrid of the dye. The resultant decrease in the ground-state level of the dye is thus quite analogous to the decrease occasioned by increasing the $-M$ effect of the nitrogenous heterocyclic system by structural changes.*

* [*Added*, Aug. 2nd, 1951.] Recently Schönberg, Mustafa, and Asker (*J. Amer. Chem. Soc.*, 1951, **73**, 2876) have shown that spirans (I) give deep colours when adsorbed on silica gel or alumina. Even (I; X = O, R = Me) gives the colour which it would be expected to show if it were thermochromic. They interpret this as a strong polarization effect favouring ionization of the spiran or as a shifting of the spiran–dye equilibrium by effective removal from solution of the traces of dye normally present. The first explanation seems the more likely and may be compared with the solvent effect. It is clear, however, since (I; X = O, R = Me) resists ionization in polar solvents, the polarizing electric field of the adsorbent is more powerful than that of such solvents, as might be expected. Consequently, the strong stabilization of all dipolar structures, particularly (II*b*), contributing to the hybrid of the adsorbed dye is apparently sufficient to lower the ground state level (Fig. 1) from a point lying between curves *Z* and *X* and above *B* to a point below *B*. These two points will not lie on curve *Z* since, as has been shown, the dye is non-planar and has consequently a higher energy than a similar, planar dye as a result of a decrease in the overlap of its π-orbitals.

The Energetic Asymmetry of the Dyes.—Wizinger and Wenning (*loc. cit.*) have reported that dyes of type (II; X = NR) which give red or blue solutions in solvents such as benzene or pyridine give orange or even yellow solutions in aqueous pyridine or aqueous alcohol. They explained these hypsochromic shifts by postulating that the addition of water to the dye molecule resulted in the formation of the benzostyryl dye hydroxide (III; $Y^- = OH^-$), the cations of which are all yellow or orange. They supported this thesis by the observation that the deep colour (red or blue) returned on addition of alkali to the yellow solutions, which they interpreted as an indication of the regeneration of (II*b*). Repetition of their experiments, however, failed to show the effect of alkali (either visually or on absorption measurements; see Table I). They also observed that the yellow or orange dye could be extracted completely from the aqueous solution by benzene, giving a blue solution, and explained this by postulating an equilibrium in the aqueous phase between the original dye and the yellow hydroxide, the equilibrium being largely towards the hydroxide. The high solubility of the original dye in benzene then provided a means of shifting the equilibrium completely in the other direction. Absorption measurements on the aqueous-alcoholic solutions of these dyes, however, show no indication of absorption in the region of the absorption band of the dye in benzene. From what follows it will be seen that this is not surprising. The most likely explanation of these phenomena is believed to be as follows.

Förster (*loc. cit.*) has shown that the theory, which explains the bathochromic shift exhibited by non-ionic dyes on increase of the solvent polarity, demands that this shift can only continue until the point of energetic symmetry (degeneracy) of the dye is attained. As the solvent polarity increases beyond this point the dye again loses its energetic symmetry, in that the dipolar extreme structure becomes more significant than the non-polar structure with a consequent hypsochromic shift. Examples of dyes exhibiting such an inversion were not available at that time, nor was Förster in a position to know the degree of non-degeneracy of the dyes he used as examples. The degree of degeneracy is now ascertainable by Brooker's deviation method (Brooker and Sprague, *loc. cit.*). It is now suggested that the dyes obtained

TABLE I.

	$\lambda_{max.}$ (mμ) in:				
Nitrogenous component in (II)	benzene	acetone	methanol	methanol–water (1 : 1)	methanol–water–NaOH
2-(3-Methylthiazolidine)	540 512	535 507	520	512	512
2-(3-Ethylbenzothiazoline)	588 551	582 545	577	565	565
2-(1-Ethyldihydroquinoline)	642 i 608	617	590	572	571
2-(1 : 3 : 3-Trimethylindoline)	—	—	570	—	—

(i = inflexion.)

TABLE II.

Nitrogenous component in (III)	$\lambda_{max.}$ (mμ), methanol–water (1 : 10)	$\lambda_{max.}$ (mμ), methanol–water (+ drop of acetic acid)
2-(3-Methylthiazoline)	497 412	412
2-(3-Ethylbenzothiazole)	566 440	441
2-(3-Ethylquinoline)	540 (inflexion) 433	433

by Wizinger and Wenning are examples showing such an inversion of shift and that the colour changes observed by these authors are manifestations of this inversion. Many other dyes showing this inversion have since been made by Brooker (unpublished work) and by the author.*

To show this inversion, absorption measurements were made on three dyes of type (II) in a number of anhydrous and aqueous solvents. Table I discloses a progressive decrease in

* Since this paper was written my attention has been drawn to papers by Kiprianov (with Petrun'kin, *J. Gen. Chem. U.S.S.R.*, 1940, **10**, 600, 613; with Timshenko, *ibid.*, 1947, **17**, 1468) on related dyes [see also work by Kuhn and Bär, *Annalen*, 1935, **516**, 155, and by Brooker and Keyes (in the press) on phthalones].

$\lambda_{max.}$ on proceeding from the non-polar benzene to the highly polar aqueous methanol. This clearly precludes the explanation of the colour shift given by Wizinger and Wenning. Moreover it is readily understandable why, even if their explanation had been correct, it would not be possible for the addition of aqueous alkali to restore the colour of the solution to that given in an anhydrous solvent such as pyridine (which gives absorption figures similar to those given in benzene).

Table II shows the absorption characteristics of the hydriodides of (II), namely, (III; $Y^- = I^-$) in aqueous methanol, and in the same solvent with a drop of acetic acid. The long-wave-length peak in aqueous methanol is considered to arise by hydrolysis, resulting in the ionization of the hydroxyl group of the salt. This band would then correspond to that of the dye (II), the hypsochromic shift from the values given in Table I being due to the lower methanol–water ratio. The second peak at shorter wave-lengths is considered to be the true peak of the cation of (III), as is confirmed by the measurements under weakly acid conditions (second absorption column) where the peaks due to ionization are suppressed. This is additional evidence against the mechanism of colour change given by Wizinger and Wenning.

Even stronger hypsochromic shifts on increase of the solvent polarity were given by dimethin*mero*cyanines derived from salicylaldehyde, its 3- and 5-nitro-derivatives, and particularly from 4-hydroxy-3-nitrobenzaldehyde (see Experimental section). This is to be expected since such structural changes will increase the dye polarity and the non-degeneracy of its resonance system (II*a*, *b*) by increasing the $+M$ effect of the ketonic moiety.

Experimental.

Analyses are by Drs. Weiler and Strauss of Oxford. M. p.s are uncorrected.

[1 : 3 : 3-*Trimethyl*-2-*indolenine*][1 : 3-*diethylhexahydro*-2-*thio*-5-*pyrimid*-4 : 6-*dione*]*dimethin*merocyanine (VII).—2-2′-Acetanilidovinyl-3 : 3-dimethylindolenine methiodide (1·25 g., 0·0025 mol.), 1 : 3-diethylthiobarbituric acid (0·5 g., 0·0025 mol.), ethanol (10 c.c.), and triethylamine (0·5 c.c.) were refluxed together for 5 minutes on the steam-bath. The crystalline dye was collected and washed with methanol. It formed orange needles (0·7 g.), m. p. 276°, from ethanol (Found: N, 10·9; S, 8·2. $C_{21}H_{25}O_3N_3S$ requires N, 10·95; S, 8·3%).

1 : 3 : 3-*Trimethyl*-6′-*nitroindoline*-2-spiro-2′-*benzopyran* (VIII).—2 : 3 : 3-Trimethylindolenine methiodide (1·5 g., 0·005 mol.), 2-hydroxy-5-nitrobenzaldehyde (0·85 g., 0·005 mol.), ethanol (10 c.c.), and piperidine (0·5 c.c.) were refluxed for 15 minutes. The intensely purple solution was concentrated to half-volume and, on chilling, large purple aggregates slowly separated. They formed a pink powder when crushed. They may be recrystallized from methanol (purple solution when hot, red on cooling) but the crystals are then coloured. The *spiran* is best recrystallized from light petroleum (b. p. 80—100°) (yellow solution), forming flat, colourless needles, m. p. 147° (blue). It gives blue solutions in pyridine or nitrobenzene, red in aqueous pyridine or cold *o*-chlorophenol, the colour changing to purple, then blue, when the last solution is heated (Found: C, 70·7; H, 5·6; N, 9·0. $C_{19}H_{18}O_3N_2$ requires C, 70·8; H, 5·6; N, 8·7%). The 8-*nitro*-isomer (1·45 g.) was similarly obtained from 2-hydroxy-3-nitrobenzaldehyde (0·85 g.) as pale yellow needles, m. p. 180°, from light petroleum (b. p. 80—100°), or soft magenta needles from ethanol (Found: N, 8·8. $C_{19}H_{18}O_3N_2$ requires N, 8·7%). It gave magenta solutions in warm aqueous–pyridine or –methanol, the colour remaining on cooling. It develops a blue colour in hot diphenyl ether.

[3-*Methyl*-2-*thiazolin*e][1 : 2-*dihydro*-2-*ketonaphthalen*e]*dimethin*merocyanine (XIII).—2-Methylthiazoline methiodide (2·33 g., 0·01 mol.), 1-formyl-2-naphthol (1·72 g., 0·01 mol.), and ethanol (20 c.c.) were warmed gently to effect dissolution, and the source of heat removed. Addition of piperidine (1 c.c.) produced a red colour, and 2-2′-(2″-*hydroxy*-1″-*naphthyl*)*vinylthiazoline methiodide* (XIII + HI; cf. III) (2·0 g.) separated. A sample formed bright yellow crystals, m. p. 226°, from acetic acid (Found: I, 31·9. $C_{16}H_{16}ONSI$ requires I, 32·0%). The crude iodide (1·9 g.) was suspended in ethanol (50 c.c.), and dissolved by addition of an excess of aqueous ammonia. Slow addition of water then caused the dye *base* (XIII) to crystallize as glittering plates. It formed red plates, m. p. 200°, from methanol (Found: N, 5·0; S, 11·85. $C_{16}H_{15}ONS$ requires N, 5·2; S, 11·9%).

3-*Methylthiazolidine*-2-spiro-2′-[3′-*methyl*-2′-*naphtho*(1′ : 2′-5″ : 6″)*pyran*] (XIV).—2-Ethylthiazoline methiodide (2·57 g., 0·01 mol.) (obtained by heating equimolar amounts of the base and methyl iodide on the steam-bath for 90 minutes), 2-hydroxy-1-naphthaldehyde (1·72 g., 0·01 mol.), ethanol (10 c.c.), and piperidine (1·0 c.c.) were warmed for 5 minutes of the steam bath. Addition of aqueous ammonia precipitated an orange oil which, after being washed with water, was extracted with hot light petroleum (b. p. 80—100°). The extract deposited colourless crystals (1·1 g.) on chilling. The *spiran* formed colourless, glassy needles, m. p. 125° from methanol. The melt became yellow at *ca.* 200° (Found: C, 72·5; H, 5·8; N, 4·6; S, 11·2. $C_{17}H_{17}ONS$ requires C, 72·1; H, 6·0; N, 4·95; S, 11·3%). Addition of 2N-hydrochloric acid to a methanol suspension gave a yellow solution (of styryl dye ?) which faded to give colourless needles. These formed glossy hairlike needles, m. p. 156°, from aqueous methanol. The same product, which is sulphur- and nitrogen-free, was obtained directly by heating 2-ethylthiazoline ethiodide and 2-hydroxy-1-naphthaldehyde in alcoholic piperidine.

3-*Ethylbenzothiazoline*-2-spiro-2′-[3-*methyl*-2-*naphtho*(1′ : 1′-5″ : 6″)*pyran*] (XII).—2-Ethylbenzothiazole ethotoluene-*p*-sulphonate (Hamer, Rathbone, and Winton, *J.*, 1947, 954) (1·85 g.), 2-hydroxy-

1-naphthaldehyde (0·85 g.), ethanol (20 c.c.), and piperidine (0·5 c.c.) were refluxed together for 30 minutes. An intense purple colour developed and crystals formed rapidly. These (1·7 g.) were collected after chilling, dissolved in hot light petroleum (b. p. 80—100°), and the solution was filtered from insoluble dark green crystals. The purple solution deposited the required *spiran* (1·0 g.) on chilling. From light petroleum it formed colourless, fluffy needles, m. p. 150° (Found: N, 3·95; S, 9·3. $C_{22}H_{19}ONS$ requires N, 4·05; S, 9·25%). The colour of the purple melt remained on cooling. It gave a weak purple colour in boiling diphenyl ether. The spiran (1·0 g.) was dissolved in ether (75 c.c.), and hydrogen chloride bubbled into the solution. The yellow oil soon crystallized and formed orange-yellow crystals, m. p. 206°, from ethanol (Found: Cl, 8·45. $C_{22}H_{20}ONSCl,C_2H_5{\cdot}OH$ requires Cl, 8·35%). It is considered to be 2-2′-(2″-*hydroxy*-1″-*naphthyl*)-1′-*methylvinylbenzothiazole ethochloride*.

[1-*Ethyl*-2-*quinoline*][4-cyclo*hexa*-2 : 4-*dienone*]*dimethin*merocyanine *Trihydrate*.—Quinaldine ethiodide (3 g., 0·01 mol.), salicylaldehyde (2·45 g., 0·02 mol.), ethanol (15 c.c.), and piperidine (0·5 c.c.) were refluxed for 30 minutes. The styryl iodide (2·6 g.) separated rapidly. It was converted into the *base trihydrate* by boiling it for 5 minutes with aqueous 2N-sodium carbonate (100 c.c.). The green crystals (2·1 g.) were collected after chilling. It formed green-black needles, m. p. 140° (decomp.), from boiling water containing a little triethylamine. The dye was dried over phosphoric oxide at 100°/10 mm. (Found: C, 69·7; H, 7·0; N, 4·2. $C_{19}H_{17}ON,3H_2O$ requires C, 69·3; H, 7·05; N, 4·25%) and had $\lambda_{max.}$ 637 mμ in pyridine and 513 mμ in aqueous methanol.

[1-*Ethyl*-2-*pyridine*][5-cyclo*hexa*-2 : 4-*dienone*]*dimethin*merocyanine *Pentahydrate*.—α-Picoline ethiodide (2·5 g., 0·01 mol.), salicylaldehyde (2·5 g.), ethanol (10 c.c.), and piperidine (0·5 c.c.) were refluxed for 1 hour and the styryl iodide was precipitated with ether as a yellow oil. It was well washed with ether, dissolved in ethanol (10 c.c.), and chilled. The orange powder (2·1 g.) which crystallized out was dissolved in aqueous 2N-sodium carbonate (25 c.c.), and the solution filtered and chilled. The yellow oily *pentahydrate* which separated crystallized rapidly. It formed red prisms, m. p. 170—180° (decomp.), from water. It was dried at 100°/10 mm. over phosphoric oxide (Found: C, 57·05; H, 7·9; N, 4·4. $C_{15}H_{15}ON,5H_2O$ requires C, 57·15; H, 7·95; N, 4·45%) and had $\lambda_{max.}$ 568 mμ in pyridine and 430 mμ in aqueous methanol.

[1-*Ethyl*-4-*pyridine*][5-cyclo*hexa*-2 : 4-*dienone*]*dimethin*merocyanine *pentahydrate* was similarly obtained from γ-picoline ethiodide. From water it formed maroon needles, m. p. 180—190° (decomp.). Drying at 10 mm. over potassium hydroxide resulted in the loss of some water of crystallization, causing the crystals to break up by bubble formation (Found: C, 57·3; H, 7·8; N, 4·35. $C_{15}H_{15}ON,5H_2O$ requires C, 57·15; H, 7·95; N, 4·45%). It had $\lambda_{max.}$ 620 mμ in pyridine and 470 mμ in aqueous methanol.

[1-*Ethyl*-2-*quinoline*][6-(2-*nitro*cyclo*hexa*-2 : 4-*dienone*)]*dimethin*merocyanine.—Quinaldine ethiodide (1·5 g., 0·005 mol.), 2-hydroxy-3-nitrobenzaldehyde (0·85 g., 0·005 mol.), ethanol (20 c.c.), and piperidine (0·5 c.c.) were refluxed for 5 minutes, causing solidification. The maroon powder (2·25 g.) was boiled with aqueous 2N-sodium carbonate, collected, washed with water, and air-dried. It formed a fine, brown, crystalline powder of indefinite m. p. from aniline–ether (Found: N, 8·7. $C_{19}H_{14}O_3N_2$ requires N, 8·75%); it had $\lambda_{max.}$ 573 mμ in pyridine and 480 mμ in aqueous methanol.

[1-*Ethyl*-2-*pyridine*][6-(2-*nitro*cyclo*hexa*-2 : 4-*dienone*)]*dimethin*merocyanine *Monohydrate*.—This was similarly obtained by refluxing α-picoline ethiodide (2·5 g.) with the aldehyde (1·7 g.) in alcoholic triethylamine for 10 minutes, followed by carbonate treatment of the resulting product (2·4 g.). From water the *dye* formed flat, golden yellow platelets, m. p. 238°, after vacuum drying during which it swelled to an orange crystalline mass (Found: C, 62·6; H, 5·4; N, 9·45. $C_{18}H_{14}O_3N_2,H_2O$ requires C, 62·5; H, 5·55; N, 9·75%); it had $\lambda_{max.}$ 507 mμ in pyridine and 431 mμ in aqueous methanol.

[1-*Ethyl*-4-*pyridine*][6-(2-*nitro*cyclo*hexa*-2 : 4-*dienone*)]*dimethin*merocyanine *dihydrate* was obtained similarly from γ-picoline ethiodide (2·5 g.) as red needles, m. p. 246° (darkens at 235°) after vacuum-drying (swells) (Found: C, 60·1; H, 5·8; N, 9·25. $C_{18}H_{14}O_3N_2,2H_2O$ requires C, 58·8; H, 5·9; N, 9·15%), and had $\lambda_{max.}$ 533 mμ in pyridine and 450 mμ in aqueous methanol.

[1-*Ethyl*-2-*quinoline*][6-(5-*nitro*cyclo*hexa*-2 : 4-*dienone*)]*dimethin*merocyanine was obtained directly (1·7 g.) by refluxing for 15 minutes a solution of quinaldine ethiodide (1·5 g.), 2-hydroxy-5-nitrobenzaldehyde (0·85 g.), and piperidine (0·5 c.c.) in ethanol (20 c.c.). It formed a brownish-green crystalline powder of indefinite m. p. from ethanol (Found: N, 8·65. $C_{19}H_{14}O_3N_2$ requires N, 8·75%), having $\lambda_{max.}$ 593 mμ in pyridine and 502 mμ in aqueous methanol.

[1-*Ethyl*-2-*pyridine*][6-(5-*nitro*cyclo*hexa*-2 : 4-*dienone*)]*dimethin*merocyanine *trihydrate* was similarly obtained from α-picoline ethiodide as red-brown crystals, m. p. 249°, after recrystallization from aqueous 2N-sodium carbonate, then from ethanol (Found: C, 55·8; H, 6·2; N, 8·4. $C_{18}H_{14}O_3N_2,3H_2O$ requires C, 55·55; H, 6·15; N, 8·6%), $\lambda_{max.}$ 545 mμ in pyridine and 468 mμ in aqueous pyridine.

[1-*Ethyl*-4-*pyridine*][6-(5-*nitro*cyclo*hexa*-2 : 4-*dienone*)]*dimethin*merocyanine *pentahydrate*, obtained similarly, formed brown crystals, m. p. *ca.* 170°, after recrystallizing from aqueous 2N-sodium carbonate, then from ethanol (Found: C, 49·7; H, 6·7; N, 7·7. $C_{18}H_{14}O_3N_2,5H_2O$ requires C, 50·0; H, 6·65; N, 7·8%), and had $\lambda_{max.}$ 570 mμ in pyridine and 479 mμ in aqueous methanol.

[1 : 3 : 3-*Trimethyl*-2-*indolenine*][4-(2-*nitro*cyclo*hexa*-2 : 5-*dienone*)]*dimethin*merocyanine.—2 : 3 : 3-Trimethylindolenine methiodide (1·5 g., 0·005 mol.), 4-hydroxy-3-nitrobenzaldehyde (0·85 g., 0·005 mol.), ethanol (10 c.c.), and piperidine (0·3 c.c.) were refluxed for 30 minutes. The solid (1·3 g.) which crystallized was boiled for 15 minutes with alcohol (250 c.c.), water (5 c.c.), and triethylamine (5 c.c.), and the crystals were collected. This was repeated and the rather insoluble dye, m. p. 252°, obtained as steel-grey crystals (Found: N, 9·0. $C_{19}H_{18}O_3N_2$ requires N, 8·7%), $\lambda_{max.}$ 558 mμ in pyridine and 505 mμ in aqueous methanol.

[*3-Ethyl-2-benzothiazole*][4-(*2-nitro*cyclo*hexa*-2 : 5-*dienone*)]*dimethin*merocyanine, prepared similarly from 2-methylbenzothiazole ethiodide (1·5 g.), formed black crystals with a gold reflex, m. p. 270°, after being repeatedly boiled with aqueous–alcoholic triethylamine (Found: N, 8·4. $C_{17}H_{14}O_3N_3S$ requires N, 8·6%). It had $\lambda_{max.}$ 563 mμ in pyridine and 486 mμ in aqueous methanol.

[1-*Ethyl*-2-*quinoline*][4-(2-*nitro*cyclo*hexa*-2 : 5-*dienone*)]*dimethin*merocyanine, similarly obtained, formed dark green crystals, m. p. 287°, from alcoholic triethylamine (Found: N, 8·4. $C_{19}H_{14}O_3N_3$ requires N, 8·75%), and had $\lambda_{max.}$ 580 mμ in pyridine and 482 mμ in aqueous methanol.

[1-*Ethyl*-2-*pyridine*][4-(2-*nitro*cyclo*hexa*-2 : 5-*dienone*)]*dimethin*merocyanine *Heptahydrate*.—α-Picoline ethiodide (2·5 g., 0·01 mol.), 4-hydroxy-3-nitrobenzaldehyde (1·7 g., 0·01 mol.), methanol (15 c.c.), and piperidine (0·5 c.c.) were refluxed for 2 hours. The solvent was removed and the oil dissolved in a little acetone. Crystals were deposited on storage. The orange needles, m. p. *ca.* 240° (decomp.) (from water), became orange-red on vacuum-drying over potassium hydroxide (Found: C, 35·6; H, 7·3; N, 6·95. $C_{15}H_{14}O_3N_2,7H_2O$ requires C, 45·3; H, 7·05, N, 7·05%). It contained no iodide ion and had $\lambda_{max.}$ 528 mμ in pyridine and 413 mμ in aqueous methanol.

[1-*Ethyl*-4-*pyridine*][4-(2-*nitro*cyclo*hexa*-2 : 5-*dienone*)]*dimethin*merocyanine *trihydrate* was similarly obtained as red-orange needles, m. p. *ca.* 245° (decomp.), from water, becoming deep maroon on drying in a vacuum over potassium hydroxide (Found: C, 55·7; H, 6·5; N, 8·6. $C_{15}H_{14}O_3N_2,3H_2O$ requires C, 55·55; H, 6·15; N, 8·65%) and having $\lambda_{max.}$ 549 mμ and 423 mμ in aqueous methanol.

The author thanks Misses A. E. Matthews and M. E. Cole for the absorption measurements and Dr. W. E. Moffitt for helpful criticism.

RESEARCH LABORATORIES,
KODAK LIMITED, WEALDSTONE, MDDX.

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674. *Amino-acids and Peptides. Part V.* Determination of* L-*Glutamic Acid by the Isotope Dilution Method.*

By C. C. BARKER, I. W. HUGHES, and G. T. YOUNG.

The accuracy of the isotope dilution method for the determination of L-glutamic acid has been examined by using synthetic mixtures of amino-acids. Individual results are within 0·7% of the theoretical, whilst the mean is 99·7% of the theoretical value. The procedure has been used to determine the L-glutamic acid formed on hydrolysis of a sample of gliadin.

OF the general methods available for the analysis of amino-acid mixtures, the " isotope dilution " procedure offers important advantages. Developed by Schoenheimer, Ratner, and Rittenberg (*J. Biol. Chem.*, 1939, **130**, 703) and by Ussing (*Nature*, 1939, **144**, 977), this method involves the addition of a known weight of isotopic amino-acid to the mixture being analysed; a pure sample of this amino-acid is then recovered by any suitable means and the change in isotope concentration is determined, from which the proportion of the amino-acid in the original mixture can readily be calculated. Normally, the isotopic amino-acid contains ^{15}N in the amino-group, in which case the isotopic concentrations are assayed in the mass spectrometer. The difficulties of quantitative isolation are avoided by this method, which should be capable of high accuracy.

Many such determinations of amino-acids in protein hydrolysates have been reported (for reviews see, *e.g.*, Shemin and Foster, *Ann. N.Y. Acad. Sci.*, 1946, **47**, 119; Tristram, *Adv. Protein Chem.*, 1949, **5**, 83). The main object of the work presented here was to examine the accuracy of this method for the determination of L-glutamic acid, by the analysis of known synthetic mixtures.

The accuracy of the isotope dilution method depends primarily on the purity of the added and the isolated samples and on the accuracy of the mass-spectrometric assays. The establishment of the purity of an amino-acid is not easy by conventional means, since a contaminant is likely to be of similar composition or even isomeric. In the past, crystallisation has been repeated until the isotopic concentration is unchanged, and such constants as nitrogen content and specific rotation have been used for confirmation. The difficulties involved are illustrated by the fact that a sample of L-glutamic acid hydrochloride, isolated from the hydrolysate of human serum albumin and recrystallised until the $^{15}N : {}^{14}N$ ratio became constant, was found still to be impure by optical-rotation measurements, containing an appreciable amount of L-cystine dihydrochloride (Shemin, *J. Biol. Chem.*, 1945, **159**, 439). The danger of co-precipit-

* Part IV, *J.*, 1951, 1745.

ation of nearly related amino-acids has been emphasised by Keston, Udenfriend, and Cannan (*J. Amer. Chem. Soc.*, 1949, **71**, 249), and there are cases where specific rotations do not differ sufficiently to enable small amounts of impurities to be detected.

We therefore developed the vapour-pressure method for the differential-solubility test of chemical purity (Hughes and Young, *Nature*, 1950, **164**, 503; Hughes, Williams, and Young, *J.*, 1951, 1279), by which contamination of one amino-acid by another, or by its enantiomorph, may be detected in amounts of the order of 0·2%. Experiments with synthetic mixtures enable a limit to be placed on the amount of amino-acid impurity which can be present in a given sample, and errors from this source may be evaluated. Application of the method to the sample of L-[^{15}N]glutamic acid hydrochloride used in this work showed that the sample could not contain more than 0·2% of L-aspartic acid hydrochloride. Although the results of the test are conveniently expressed in this manner, it is likely that part at least of the vapour-pressure difference is due to occluded hydrogen chloride, to which the test will be highly sensitive.

Three synthetic mixtures were prepared and analysed: (*A*) L-glutamic acid hydrochloride, DL-glutamic acid hydrochloride, and L-aspartic acid hydrochloride; (*B*) as above, with the addition of DL-alanine and L-lysine hydrochloride; (*C*) as in (*B*), with the further addition of glycine and L-tyrosine. The relative amounts approximated to those found in insulin. After addition of isotopic L-glutamic acid hydrochloride, basic amino-acids (if present) were precipitated with phosphotungstic acid, and the acidic amino-acids were removed on "Amberlite" IR4—B" anion-exchange resin. L-Glutamic acid was finally isolated as the hydrochloride. Recrystallisation was continued until the differential solubility test gave a difference in pressure corresponding to the presence of less than 0·2% of L-aspartic acid hydrochloride. A portion of the material was then converted into ammonium chloride by the Kjeldahl method and thence into nitrogen by the action of sodium hypobromite. The recrystallisation of the L-glutamic acid hydrochloride was then continued, and samples were converted into nitrogen at each stage.

The mass-spectrometric determinations on the nitrogen samples were carried out at the Atomic Energy Research Establishment, Harwell. The ^{15}N concentrations were calculated from the relative intensities of the peaks at mass numbers 28 and 29 ($^{14}N^{15}N^+$); this calculation assumes equilibrium to be established in the reaction $^{14}N^{14}N + {}^{15}N^{15}N \rightleftharpoons 2\,{}^{14}N^{15}N$, and the equilibrium constant $\frac{[^{14}N^{15}N]^2}{[^{14}N^{14}N][^{15}N^{15}N]}$ to be 4·00. The relative intensities at mass numbers 32 (O_2^+) and 40 (A^+) were also recorded, in order to determine contamination by air; appropriate corrections were then applied to the peaks at masses 28 and 29. The relative intensity at mass 44 was used to determine carbon dioxide, and a correction (for CO^+) was similarly applied to the peaks at masses 28 and 29. The relative intensity of the peaks at masses 28 and 32 for a sample of air was 5·4 : 1. The relative intensity of the peaks at masses 44 and 28 for a sample of carbon dioxide was 10 : 1.

TABLE I.

Synthetic mixture	L-Glutamic acid hydrochloride present, g.	L-[^{15}N]Glutamic acid hydrochloride added, g.	No. of crystns. of isolated sample	L-Glutamic acid hydrochloride found, g.	%	
A	1·1294	0·1208	5	1·1305	100·10	
			6	1·1311	100·14	Mean 100·1
			7	1·1291	99·97	
B	0·4012	0·0488	5	0·3985	99·33	
			6	0·3977	99·13	Mean 99·3
			7	0·3990	99·45	
C	0·9064	0·0923	5	0·9036	99·69	
			6	0·9022	99·54	Mean 99·7
			7	0·9057	99·92	

The results are summarized in Table I. It will be seen that individual assays are within 0·7% of the theoretical, whilst the mean of the three (99·7%) is considerably closer.

Professor A. C. Chibnall kindly made available a sample of gliadin from a batch in which the L-glutamic acid had previously been determined both by the gravimetric method and by the specific decarboxylase procedure (Chibnall, *J. Int. Soc. Leather Trades' Chem.*, 1946, **30**, 11; Gale, *Biochem. J.*, 1945, **39**, 46). We hydrolysed a portion in the standard manner and determined the L-glutamic acid in the hydrolysate by the isotope dilution method. The results are shown in Table II: our mean value (23·7) for the L-glutamic-acid-nitrogen, expressed as a percentage of the total-protein-nitrogen, agrees remarkably closely with the values given by

Chibnall (23·7) and Gale (23·4). These figures do not of course take into account the possibility of destruction or racemisation of the L-glutamic acid during hydrolysis, and attempts are now being made to investigate this aspect of the problem.

TABLE II.

Experiment	Gliadin, g.	L-[^{15}N]Glutamic acid hydrochloride added, g.	No. of crystns. of isolated sample	Atoms-% excess ^{15}N	L-Glutamic acid found, g. per 100 g. of gliadin *	L-Glutamic acid found, N, % of protein-N
i	1·3030	0·0710	4 (*a*)	1·503	44·04	23·70
			(*b*)	1·490		
			5 (*a*)	1·490	44·23	23·81
			(*b*)	1·490		
			6	1·498	43·99	23·67
				Mean	44·1	23·7
ii	0·7744	0·1668	4 (*a*)	4·576	43·92	23·63
			(*b*)	4·574		
			5 (*a*)	4·567	44·22	23·79
			(*b*)	4·539		
			6	4·576	43·90	23·62
				Mean	44·0	23·7

* Calc. on a dry, ash-free basis.

EXPERIMENTAL.

L-[^{15}N]*Glutamic Acid Hydrochloride.*—Reduction of α-ketoglutaric acid by hydrogen and palladium black in the presence of ammonia containing approximately 15 atoms-% excess of ^{15}N, according to Schoenheimer's method (*J. Biol. Chem.*, 1939, **127**, 301), gave DL-[^{15}N]glutamic acid hydrochloride (80—85%). Resolution was effected by the fractional crystallisation of the strychnine salts of the N-benzoyl derivative (Fischer, *Ber.*, 1899, **32**, 2468). Subsequent hydrolysis and repeated recrystallisation gave L-[^{15}N]-glutamic acid hydrochloride [Kjeldahl-N, 9·5%. Differential solubility test (see Part III, *loc. cit.*): 0·1 g. and 1·0 g., respectively, in water (0·1 c.c.) at 45° gave a vapour pressure difference of 5 mm. of oil (d^{20}, 0·80)].

Determination of L-Glutamic Acid Hydrochloride in Synthetic Mixtures.—(*A*) A solution of L-glutamic acid hydrochloride (1·1294 g.), DL-glutamic acid hydrochloride (0·003 g.), L-aspartic acid hydrochloride (0·008 g.), and L-[^{15}N]glutamic acid hydrochloride (0·1208 g.) in water (15 c.c.) was made acid to Congo-red with hydrochloric acid. Amberlite IR—4B (analytical grade) was crushed and washed with water (1 l.), 3% hydrochloric acid (500 c.c.), 3% sodium carbonate solution (500 c.c.), and finally water (4 l.). The treated Amberlite (4 g.) was added to the solution of amino-acids, which was left, with frequent shaking, for 1½ hours, after which the solution was barely acid to Congo-red. The resin was removed by filtration, and the filtrate made acid to Congo-red and retreated with fresh Amberlite (5 g.). The extraction was repeated 4 times using 6, 7, 8, and 8 g. respectively of resin. The combined Amberlite samples were then eluted for 2 hours with water (20 c.c.) kept acid to Congo-red with hydrochloric acid. The resin was then filtered off and eluted a further 4 times. The combined acidic liquors were evaporated to dryness at 50—60° under reduced pressure. The resulting syrupy mass was dissolved in the minimum of water, treated with charcoal, filtered, and saturated at 0° with hydrogen chloride. When the mixture was kept overnight in a refrigerator a crystalline mass separated; this was filtered off, washed, and dried (0·85 g.). The crude L-glutamic acid hydrochloride was recrystallised from 5N-hydrochloric acid in all-glass apparatus. The product was filtered off through a sintered-glass funnel, washed repeatedly, and recrystallised. A small sample from each recrystallisation was transferred to a vacuum-desiccator containing sodium hydroxide pellets and calcium chloride. Each sample was tested for purity in the differential tensimeter, and after the third recrystallisation the vapour-pressure difference for successive samples was nearly constant. Crystallisation was repeated 7 times in all. (All differential-solubility tests on isolated samples were carried out with 0·02 and 0·10 g. respectively of material in 0·01 c.c. of water at 45°.)

No. of crystallisations	4	5	6	7
Yield (based on crude wt.), %	66	50	44	24
V. p. difference (mm. of oil)	4	3	3	3

(*B*) The mixture contained L-glutamic acid hydrochloride (0·4012 g.), DL-glutamic acid hydrochloride (0·005 g.), L-aspartic acid hydrochloride (0·08 g.), L-lysine hydrochloride (0·02 g.), DL-alanine (0·03 g.), and L-[^{15}N]glutamic acid hydrochloride (0·0488 g.). A solution of the mixture in water (15 c.c.) was made acid to Congo-red and heated to 70°. Ether-soluble phosphotungstic acid (2·0 g.) in water (1·5 c.c.) was then added. On the mixture being kept overnight, a heavy white precipitate settled out, which was filtered off. The filtrate was again made acid to Congo-red and treated with 5% phosphotungstic acid solution. After 2—3 hours, a faint precipitate appeared, which was removed by filtration. Further addition of phosphotungstic acid solution gave no precipitate.

The solution was then washed with butanol–ether (1 : 1) (6 × 30 c.c.). The aqueous layer was evaporated to dryness under diminished pressure, water (10—15 c.c.) added, and the solution made

acid to Congo-red. The amino-dicarboxylic acids were isolated with Amberlite IR—4B, as previously described. Isolation and recrystallisation of L-glutamic acid hydrochloride proceeded as before (crude yield, 0·39 g.).

No. of crystallisations	4	5	6	7
Yield (based on crude wt.), %	65	52	45	39
V. p. difference (mm. of oil)	6	4	4	4

(*C*) The mixture consisted of L-glutamic acid hydrochloride (0·9064 g.), DL-glutamic acid hydrochloride (0·003 g.), L-aspartic acid hydrochloride (0·08 g.), L-lysine hydrochloride (0·02 g.), DL-alanine (0·04 g.), glycine (0·02 g.) and L-[^{15}N]glutamic acid hydrochloride (0·0923 g.). L-Glutamic acid hydrochloride (0·755 g.) was isolated as described for mixture (*B*) and recrystallised 7 times.

No. of recrystallisations	4	5	6	7
Yield (based on crude wt.), %	74	62	47	35
V. p. difference (mm. of oil)	4	3	3	3

Preparation of Nitrogen Samples from L-Glutamic Acid Hydrochloride.—Each sample of L-glutamic acid hydrochloride (*ca.* 25 mg.) was converted into ammonia by the modified Kjeldahl procedure and then oxidised to nitrogen with sodium hypobromite according to Rittenberg's method (" Preparation and Measurement of Isotopic Tracers," Edwards, Ann Arbor, Michigan, 1947). We have found it essential to take great care to remove dissolved gases from the solutions before allowing them to react.

Samples of normal nitrogen were similarly prepared from " AnalaR " ammonium chloride. The mass-spectrometric determinations were carried out by Mr. Palmer and his colleagues at the Atomic Energy Research Establishment, Harwell.

The amount of L-glutamic acid hydrochloride (*X*) in the original mixture was calculated from the formula $X = A[C_0/C) - 1]$, where *A* is the amount of L-[^{15}N]glutamic acid hydrochloride added and C_0 and *C* are the atoms-% excess of ^{15}N in the added and the isolated material respectively.

The mass-spectrometer readings for the determination of L-glutamic acid hydrochloride in the synthetic mixtures are recorded in Table III and the calculated results of the analyses in Table I.

TABLE III.

Relative intensity of peaks.*

	Observed mass 28	Observed mass 29	Observed mass 32	Observed mass 44	Corrected mass 28	Corrected mass 29	Atoms % ^{15}N	Atom-% excess ^{15}N
Synthetic mixture (*A*).								
Normal nitrogen	100	0·7342	0·08	1·16	99·452	0·7298	0·3656	—
L-[^{15}N]Glutamic acid hydrochloride	100	35·449	0·74	0·96	95·908	35·419	15·587	15·221
Normal nitrogen	100	0·7316	0·08	0·54	99·514	0·7279	0·3644	—
L-Glutamic acid hydrochloride isolated :								
5th recrystn.	100	3·6417	0·56	1·20	96·856	3·6185	1·8337	1·469
6th "	100	3·6834	0·30	0·92	98·288	3·6706	1·8331	1·469
7th "	100	3·6659	0·44	0·54	97·570	3·6481	1·8353	1·471
Synthetic mixture (*B*).								
Normal nitrogen	100	0·7386	0·17	0·86	98·996	0·7310	0·3679	—
L-[^{15}N]Glutamic acid hydrochloride	100	35·710	0·59	1·53	96·661	35·685	15·583	15·215
LGlutamic acid hydrochloride isolated :								
5th recrystn.	100	4·0699	0·36	1·03	97·953	4·0547	2·0278	1·660
6th "	100	4·0816	0·33	1·01	98·117	4·0676	2·0308	1·663
7th "	100	4·0783	0·30	0·73	98·307	4·0658	2·0261	1·658
Synthetic mixture (*C*).								
Normal nitrogen	100	0·7344	0·15	1·15	99·075	0·7273	0·3657	—
L-[^{15}N]Glutamic acid hydrochloride	100	34·781	0·71	1·30	96·036	34·752	15·321	14·955
L-Glutamic acid hydrochloride isolated :								
5th recrystn.	100	3·4404	0·80	1·00	95·580	3·4080	1·7516	1·386
6th "	100	3·4435	0·80	1·60	95·520	3·4104	1·7539	1·388
7th "	100	3·4497	0·70	1·10	96·110	3·4211	1·7487	1·383

* The relative intensity of the peak at mass 40 (A^+) never exceeded 0·01.

Determination of L-Glutamic Acid in Gliadin.—The sample of gliadin had 17·69(9)% Kjeldahl-N, corrected for 9·8% moisture and 0·86% ash.

(i) From gliadin (1·3030 g.), hydrolysed with hydrochloric acid, L-glutamic acid hydrochloride (0·62 g.) was isolated and recrystallised in the usual manner.

No. of recrystallisations	4	5	6
Yield (based on crude wt.), %	65	50	32
V. p. difference (mm. of oil)	3	2	3

(ii) Concentrated hydrochloric acid (3·8 c.c.) was added to gliadin (0·7744 g.) and left at room temperature for 16 hours, complete dissolution occurring. Water (2·79 c.c.) was added to the solution which was then heated for 24 hours under reflux.

L-[^{15}N]Glutamic acid hydrochloride (0·1668 g.) was added to the solution which was again heated for 1½ hours. The solution was then evaporated to dryness at 50—60° under reduced pressure and the residual solid dissolved in water (10 c.c.). L-Glutamic acid hydrochloride (0·37 g.) was isolated as already described and recrystallised 6 times.

No. of recrystallisations	4	5	6
Yield (based on crude wt.), %	71	55	48
V. p. difference (mm. of oil)	5	3	3

The samples of L-glutamic acid hydrochloride were converted into nitrogen in the usual manner. The results of the analyses are recorded in Table II; the added L-[^{15}N]glutamic acid hydrochloride had 14·964 atoms-% excess of ^{15}N. The corrections for air and carbon dioxide were similar in magnitude to those shown in detail in Table III.

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Department of Chemistry, Bristol University.
The Dyson Perrins Laboratory, Oxford University. [*Received, July 6th*, 1951.]

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675. *The Halides of Niobium (Columbium) and Tantalum. Part III.* The Vapour Pressures of Niobium (Columbium) and Tantalum Pentafluorides.*

By Fred Fairbrother and William C. Frith.

Measurements have been made, by a static method using a Bourdon-type sickle gauge and by boiling-point determinations under a number of controlled pressures, of the vapour pressures of niobium† and tantalum pentafluorides: m. p.s: NbF_5, 80·0°; TaF_5, 95·1°; b. p.s (760 mm.): NbF_5, 234·9°; TaF_5, 229·2°. The tantalum pentafluoride, like the pentachloride and pentabromide, is more volatile than the corresponding niobium compound. The Trouton constants of all seven pentahalides examined are given and suggest some association in the liquid state.

A mixture of the fluorides prepared directly by fluorination of commercial ferrocolumbium is an excellent Friedel–Crafts-type catalyst.

The only previously reported estimates of the vapour pressures of these fluorides appear to be those derived from the boiling-point determinations carried out by Zedner and Schiller (*Ber.*, 1909, **42**, 492) and the vapour-pressure measurements by Ruff and Schiller (*Z. anorg. Chem.*, 1911, **72**, 329) carried out over a range of temperature of some 40—50° below the boiling point at 760 mm. The latter authors reported the boiling points of niobium† and tantalum pentafluorides at 760 mm. to be respectively 217—220° (corr.) and 229·2—229·5° (corr.), thus indicating that the niobium pentafluoride was more volatile than the tantalum pentafluoride. It was, however, shown in Part I of this series (*J.*, 1949, S 223) that niobium pentachloride and pentabromide were both less volatile than the corresponding tantalum compounds, and the present work shows that similarly it is the niobium pentafluoride which has the higher boiling point.

Direct measurements have now been made of the vapour pressures of both pentafluorides over a wider range of temperature by a static method using a sickle gauge, and confirmed and extended over the upper end of the temperature range by determinations of the boiling points at controlled pressures.

The measurement of the vapour pressures of these compounds presents some special difficulties on account of their extreme susceptibility to moisture and the reactivity of the hydrogen fluoride produced by hydrolysis. Ruff and Schiller (*loc. cit.*) attempted to overcome

* Part II, *J.*, 1949, 2472.

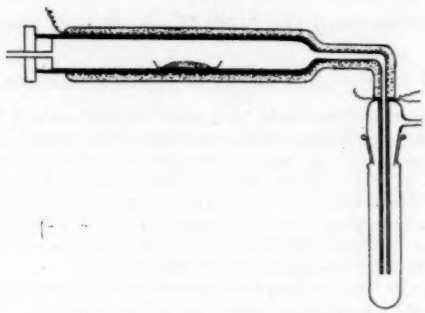
† The change from "columbium," as used in Parts I and II, to "niobium" in the present paper is in accord with a recent ruling of the Council of the Society.

these difficulties by using a copper vessel in the vapour-pressure method of Smith and Menzies (*J. Amer. Chem. Soc.*, 1910, **32**, 907). In this method the fluoride was introduced into a copper vessel with a narrow glass exit tube immersed in a bath of molten paraffin above which the pressure could be controlled and varied: the pressure at which the reference meniscus of paraffin near the tip of the glass tube neither rose nor fell was taken as the vapour pressure at the particular temperature. They observed that as the temperature was raised the halides were decomposed by the hot paraffin with the formation of brownish or black products. Moreover, as their method of introducing the fluoride into the copper vessel would probably not have excluded moisture, and as we have found with most of these solid halides, the hydrolysis by moist air is not instantaneous but occurs progressively on warming, probably through the decomposition of an intermediate hydrate, it is to be expected that in this method the vapour in the copper vessel would contain also some hydrogen fluoride, thus simulating a higher vapour pressure than the actual value. This source of error should have the most effect with the more easily hydrolysable niobium pentafluoride, and it may be seen that it is here that Ruff and Schiller's results show the greatest divergence from the present values.

Experimental.

Preparation of the Fluorides.—A few preliminary determinations were carried out with samples kindly prepared for us by Imperial Chemical Industries Limited, Alkali Division. Attempts were also made to fluorinate tantalum by heating it with silver bifluoride: these were unsuccessful, the silver bifluoride appearing to dissociate with loss of fluorine at temperatures at which the fluorination of the

Fig. 1.



metal was slow. The majority of the determinations were carried out with specimens made by direct fluorination of the pure metals in the apparatus shown in Fig. 1. Fluorine, generated by electrolysis at a rate of about 4 l. per hour, in a 10-ampere medium-temperature cell (I.C.I. Ltd.), was purified by passage through a tube containing sodium fluoride pellets at −80° to remove hydrogen fluoride, diluted with an approximately equal volume of dry oxygen-free nitrogen, and passed over 5—6 g. of pure metal in powder form, mixed with about 0·1 g. of aluminium powder and contained in a nickel boat in the heated Monel-metal reactor. The copper exit tube was heated electrically to about 150° to prevent obstruction by solidified fluoride, which was condensed in a conventional form of "trap" cooled at −80° and protected on the exit side by a drying tube. The reactor was heated initially to about 250° and the fluorination of the metal was usually completed in about 3 hours.

The trap, containing the crude product, was then quickly transferred into the wide end of a sublimation chain, as described in Part I (*loc. cit.*), which was then sealed by fusion. During this process a slow stream of dry nitrogen was passed through the sublimation chain, up to the final moment of the sealing process, in order to prevent any diffusion of atmospheric moisture into the fluoride. Fractional sublimation and transference to small hook-ended vacuum-opening ampoules then proceeded in substantially the same manner as described for the chlorides and bromides in Part I, the sublimation chain being tilted through an angle of 5—10° to the horizontal to reduce the risk of any molten fluoride flowing along the chain: melting usually occurred only in about the first four stages of fractionation, the solid subliming without melting in the later stages even though the external temperature of the tube was slightly above the m. p.

Vapour-pressure Measurements.—Measurements of the vapour pressure of tantalum pentafluoride, which were carried out first, were made in essentially the same manner as described in Part I, with the exception that corrections for pressure due to hydrolysis proved to be much more difficult. It has already been noted that it is not possible, even after careful out-gassing of the apparatus, to seal up the glass apparatus finally without disengaging a minute amount of water vapour from the molten

glass around the seal. But whereas in the case of the other halides this gives rise, on subsequent heating of the apparatus, to only a small amount of hydrogen halide which remains constant and can be easily allowed for, in the case of the fluorides the " residual pressure " observed on cooling the gauge appeared to increase steadily with both increase of temperature and time of heating. This increase, which is shown in Fig. 2, would appear to be due to the continuous formation of silicon tetrafluoride from the tantalum pentafluoride and the glass, in which the water acts as a catalyst, with the ultimate formation of tantalum entoxide with or without the intermediate formation of an oxyfluoride, *e.g.*,

$$4TaF_5 + 10H_2O = 2Ta_2O_5 + 20HF$$
$$20HF + 5SiO_2 = 5SiF_4 + 10H_2O$$

The formation of silicon tetrafluoride was confirmed by observing the temperature at which it could be condensed to a solid and the " residual pressure " removed. As may be seen from Fig. 2, the effect of this continuous hydrolysis may be very serious at the higher temperatures. It was taken into account in calculating the actual vapour pressures, by observing the rate of increase of " residual pressure " at the particular temperature of measurement and by cooling the gauge and contents as quickly as possible, after an observation, to room temperature, at which the hydrolysis is negligible. The additional correction for the effect of further hydrolysis during this cooling, which required about 10 minutes, was never more than 5 mm. and was negligible for measurements carried out at temperatures below 130°.

In an endeavour to reduce this progressive hydrolysis in the case of niobium pentafluoride, which as shown in Fig. 2 hydrolyses much more rapidly than tantalum pentafluoride, measurements of the

FIG. 2.

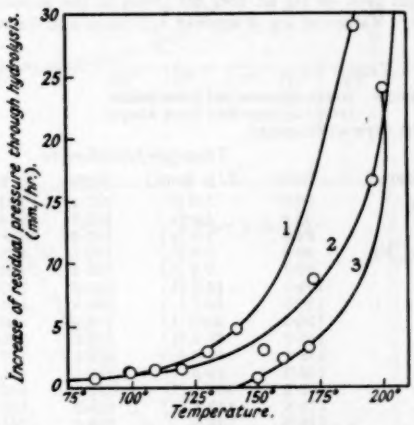


FIG. 3.

1. NbF_5 (*bare-glass gauge*). 2. TaF_5. 3. NbF_5 (*nickel-plated gauge*).

vapour pressure near the b. p. were carried out in an apparatus of similar construction but in which the whole of the interior of the gauge chamber and sickle were plated with a thin film of nickel. The purified specimen of halide, in its hook-ended container, was introduced into, and distilled from, an unplated kind of ante-chamber, which was then sealed off, so that in the end the only bare glass in contact with the fluoride vapour was the few mm. length in the neighbourhood of the final glass seal. This procedure greatly reduced, but did not entirely prevent, progressive hydrolysis: its advantages were more apparent at the lower temperatures. The thin film of nickel, deposited on the glass by the thermal decomposition of nickel tetracarbonyl, was on the average about 10^{-4} mm. thick and did not diminish the sensitivity of the gauge.

Further precautions and minor changes in design of the gauge were necessary in the case of niobium pentafluoride in order to prevent any solidification of the molten fluoride in narrow spaces or where the glass was thin.

The polymorphism of solid niobium pentabromide and pentachloride has already been noted in Part I: these are obvious since they involve visible changes in colour and crystalline form as well as, at all events in the case of the chloride, detectable changes in the vapour pressure–temperature relation. There is also some evidence of polymorphism in the case of solid niobium pentafluoride which is less easy to demonstrate since the solid remains white throughout and its vapour pressure is too small for any transition to be detected by the present method. On the other hand, it was repeatedly observed that when a mass of niobium pentafluoride which had been melted and allowed to solidify was heated, loud cracks could be heard when the temperature was still some distance below the m. p., the glass tube in which it was contained being itself not infrequently broken: much trouble

was experienced on this account. Also, when a sample was allowed to solidify in a melting-point tube, the tube was suddenly shattered on re-heating to about 20° below the m. p., whilst loose crystals in a melting-point tube seemed to become more translucent above about 60°.

Boiling-point Method.—Owing to the difficulties caused by hydrolysis of the fluorides, as noted above, measurements of the vapour pressures near the b. p. and for some distance below were confirmed and extended by determinations of the actual b. p. s at a number of different pressures. In this method, some 10 g. of purified halide were sublimed *in vacuo* into the boiling-point apparatus (Fig. 3) through the lower end, which was then sealed off, and the upper part of the apparatus was filled with dry nitrogen. The halide was heated electrically and allowed to reflux gently over the thermocouple well T which contained the same double-junction chromel–alumel thermocouple used in the measurements with the sickle gauge. The upper part of the apparatus was heated to about 110° to prevent solidification of the condensed fluoride, and connected to the same manometer and pressure-adjusting device as used for the pressure balance with the sickle gauge. Owing to the large volume of this part of the system, there was no difficulty in maintaining a constant pressure over the boiling halide: any hydrogen fluoride or silicon tetrafluoride produced by hydrolysis simply replaced part of the nitrogen as supernatant gas and was excluded from the rest of the pressure system by a trap cooled in liquid nitrogen. Boiling was continued under a given pressure until a constant temperature was reached and maintained. This method was limited to temperatures above about 160°, since below this temperature much vigorous "bumping" of the boiling halide took place. Niobium pentafluoride, once having been melted in the apparatus, was not allowed to solidify again between measurements on account of the risk of fracture of the tube on re-melting, mentioned above.

Discussion.

The vapour-pressure measurements (in mm. of Hg at 15°) are given in the accompanying table and in the curves of Figs. 4 and 5. Values of log p against $1/T$ have also been plotted

Table I.

r.: Bourdon-type sickle gauge; temp. approached from below.
f.: ,, ,, temp. approached from above.
Ni: Nickel-plated Bourdon-type sickle gauge.

Niobium pentafluoride				*Tantalum pentafluoride*			
Temp.	V. p. (mm.)	Temp.	V. p. (mm.)	Temp.	V. p. (mm.)	Temp.	V. p. (mm.)
67·5°	1·0 (f.)	190·8°	205·8 (r.)	80·0°	1·0 (f.)	182·1°	191·4 (r.)
75·4	2·0 (r.)	192·5	236·7	80·0	2·0 (r.)	183·3	214·4
83·0	3·1 (f.)	199·3	289·1	84·5	1·7 (r.)	187·3	237·7 (f.)
99·2	7·3 (r.)	201·2	294·4 (r., Ni)	89·8	3·6 (f.)	192·1	282·7
108·8	11·4 (f.)	205·8	340·3	99·7	7·8 (r.)	196·4	307·3 (r.)
118·2	17·9 (r.)	210·5	390·9	109·1	14·6 (f.)	199·1	337·7
129·7	27·6 (f.)	215·0	451·2	120·9	20·7 (r.)	200·9	334·6 (f.)
142·1	43·1 (r.)	219·0	506·4	136·5	38·0 (f.)	203·9	393·1
152·2	57·7 (r., Ni)	222·4	563·7	147·5	61·3 (f.)	206·4	410·4
160·3	81·6 (f., Ni)	225·0	614·3	152·3	67·2 (r.)	208·5	417·3 (r.)
170·7°	118·8 (r., Ni)	228·6	660·3	160·7	99·5	212·2	491·0
181·8	176·7 (f., Ni)	232·0	723·9	162·2	105·3 (f.)	223·4	642·0
184·3	192·1	—	—	172·5	143·4 (r.)	228·2	733·7
				175·9	165·0	228·8	741·9

Compound	M. p.	B. p. (760 mm.)	L_v, kcals.	Vapour pressure
NbF_5	80·0°	234·9°	12·9	$\log p_{mm.} = 8·439 - 2·824/T$
TaF_5	95·1	229·2	13·0	$\log p_{mm.} = 8·524 - 2·834/T$

in Figs. 6 and 7: from these the latent heats of volatilisation have been calculated by the Clausius–Clapeyron equation. Owing to the low volatility of the solid fluorides and the short range of vapour-pressure measurements over the solids it was not possible to derive accurate values for the molar heats of sublimation by this method. The values obtained by Ruff and Schiller (*loc. cit.*) have been included for comparison in Figs. 4 and 5, and the corresponding values of log p and $1/T$ calculated from them in Figs. 6 and 7.

It may be observed that the vapour pressures of these two fluorides are very close over much of the temperature range up to their boiling points, but that at any particular temperature the vapour pressure of niobium pentafluoride is *less* than that of tantalum pentafluoride. The separation, however, is so small in the lower ranges of temperature as to make it very difficult to represent them on a common diagram.

The difference between the physical properties of the corresponding halides of these two elements becomes therefore progressively less as the halogen becomes smaller, in all cases, however, the niobium halide being the less volatile, except perhaps in the case of the iodides for which no comparison can be made since that of niobium is too unstable to sublime. The

FIG. 4.

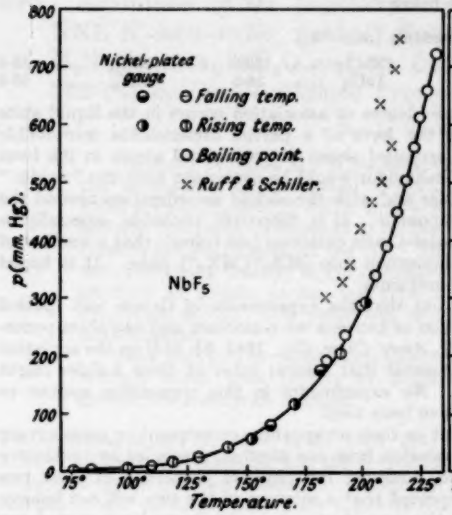


FIG. 5.

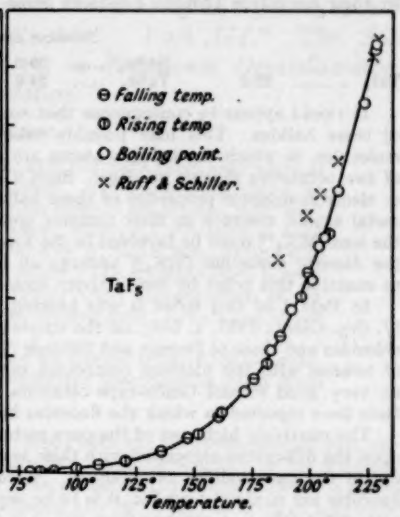


FIG. 6.

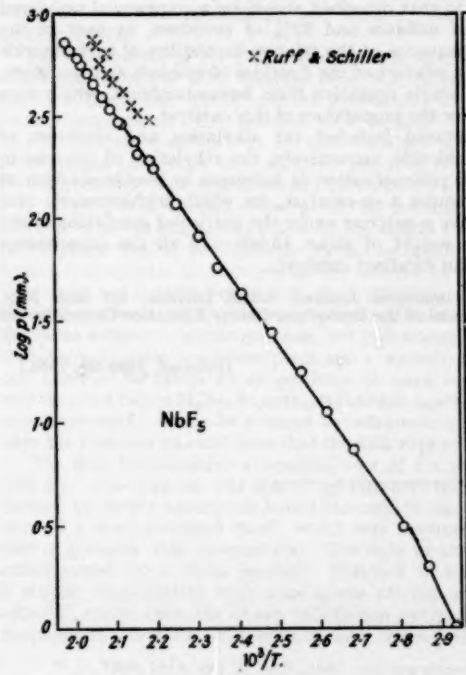
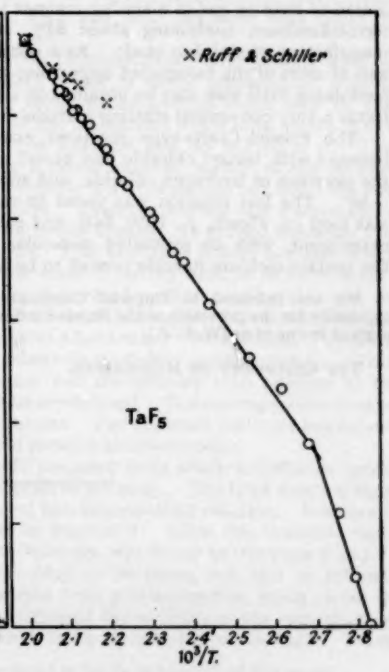


FIG. 7.



entropy change accompanying volatilisation of each of the liquid halides is high, as is shown by their respective Trouton constants given below:

Trouton constants (cals./°K.)

		$NbBr_5$ ..... 29·5	$NbCl_5$ ..... 25·0	NbF_5 ..... 25·4
TaI_5 ..... 22·2		$TaBr_5$ ..... 24·0	$TaCl_5$ ..... 26·5	TaF_5 ..... 25·9

It would appear in consequence that some degree of association occurs in the liquid state of these halides. This may possibly take the form of a partial dimerisation into double molecules, in which the halogen atoms are arranged about the two metal atoms in the form of two octahedra sharing an edge. Such a behaviour would be consistent with the "acidic" or electron-acceptor properties of these halides and with the sixfold co-ordination around the metal atoms, common in their complex compounds. It is, moreover, probable, especially as the ions $[MX_6^-]$ must be involved in the Friedel–Crafts catalyses (see below), that a number of the dimeric molecules $[MX_5]_2$ undergo an ionisation into $[MX_4^+][MX_6^-]$ pairs. It is hoped to examine this point by conductivity measurements.

In Part I of this series it was pointed out that the experiments of Grosse and Ipatieff (*J. Org. Chem.*, 1937, **1**, 559), on the ethylation of benzene with niobium and tantalum pentachlorides and those of Dermer and Billmeir (*J. Amer. Chem. Soc.*, 1942, **64**, 464) on the acylation of toluene with the niobium compound suggested that several other of these halides might be very good Friedel–Crafts-type catalysts. No experiments in this connection appear to have been reported in which the fluorides have been used.

The relatively high cost of the pure metals or their compounds, consequent to some extent upon the difficulties associated with their separation from one another, precludes any extensive use of the pure halides as catalysts. Since, however, the physical properties of these two fluorides are so closely similar, it is to be expected that a mixture of the two will not behave very differently as a catalyst from either in the pure state. Accordingly we have carried out several typical Friedel–Crafts-type reactions, using a mixture containing about 70% of NbF_5 and 30% of TaF_5, which we may call tantalo-niobium fluoride, and which was made by the action of fluorine gas in a similar manner to that described above, on a commercial powdered ferrocolumbium containing about 52% of niobium and 22% of tantalum, as used in the manufacture of stainless steels. As a consequence of the relative involatility of ferric fluoride and of most of the fluorinated impurities, a mixture of the fluorides of niobium and tantalum, containing little else, can be obtained in a single operation from ferrocolumbium, which thus forms a very convenient starting material for the preparation of this catalyst.

The Friedel–Crafts-type reactions examined included the alkylation and acylation of benzene with benzyl chloride and acetyl chloride, respectively, the ethylation of benzene in the presence of hydrogen chloride, and the polymerisation of *iso*butene in hexane solution at −80°. The last reaction was found to require a co-catalyst, for which trichloroacetic acid was used (cf. Plesch, *J.*, 1950, 543), and gave a polymer under the particular conditions of the experiment, with an estimated molecular weight of about 10,000. In all the experiments the tantalo-niobium fluoride proved to be an excellent catalyst.

We are indebted to Imperial Chemical Industries Limited, Alkali Division, for their help, especially for the provision of the fluorine cell, and to the Derbyshire County Education Committee for a grant to one of us (W. C. F.).

THE UNIVERSITY OF MANCHESTER. [*Received, June 5th*, 1951.]

676. *Separation of the Lanthanons with the Aid of Ethylenediamine-NNN'N'-tetra-acetic Acid ("Enta" Acid). Part III.* The Salt $H_4Na_4Ln_4enta_8,24H_2O$ and its Use* (a) *in Fractional Crystallisation, and* (b) *in Double-sulphate Precipitation.*

By J. K. Marsh.

The easily prepared salt $H_4Na_4Ln_4enta_8,24H_2O$ gives a rapid separation of the lanthanons by fractional crystallisation. An equilibrium, such as $4Na[Ln\ enta],H_4enta \rightleftarrows 3HLn\ enta + Na[Ln\ enta] + Na_3H\ enta$, with solid solution occurring, is believed to be the reason, HLn enta collecting in head crystals and Na[Ln enta] at the tail. Stability of $H_4Na_4Ln_4enta_8,24H_2O$ falls with decreasing basicity in the lanthanon series. The crystallisation is most effective for middle earths, but gives a rapid, rough concentration of the ytterbium earths. The potassium salt is isomorphous, but its use is not advantageous.

Small amounts of neodymium have been eliminated from $H_4Na_4Gd_4enta_8$ solution much more rapidly by double-sulphate precipitation than from gadolinium trichloride solution.

Two previous papers (*J.*, 1950, 1819; 1951, 1461 *) dealt with the use of ammonium enta as a solvent for lanthanon oxalates, and the crystallisation of a resulting complex, or the fractional reprecipitation of dissolved oxalate by addition of more oxalic acid, a mineral acid, or a simple lanthanon salt solution. Any other insoluble lanthanon salt taken into solution as a complex might prove an alternative to oxalate. The insoluble, normal enta salts, HLn enta, present a rather special case. The lanthanum and neodymium salts were prepared by Brintzinger, Thiele, and Muller (*Z. anorg. Chem.*, 1943, **251**, 285). The yttrium salt, $Y_4enta_8,24H_2O$, was found to be soluble (Brintzinger and Munkelt, *ibid.*, 1948, **256**, 65). All three were found to be simple salts.

(a) *Preparation of the Salt and its use in Fractional Crystallisation.*—The present work is concerned with the salt, $4Na[Ln\ enta],H_4enta,24H_2O$, which is easily prepared by boiling together lanthanon oxide, sodium hydroxide, and ethylenediaminetetra-acetic acid in the correct proportions. It is believed to be formed by all the lanthanons but is most stable in the cerium group. Possibly one or two members at the lutetium end do not form it. The isomorphous potassium salt has been prepared from a crude mixture, mainly of cerium and terbium earths. The potassium salt differs only very slightly from the sodium salt but it did not give as good a separation of the earths on fractionation. Even the sodium salt fractionation however is not as efficient as that with the double magnesium nitrate. In general character the salt is rather similar to the simple acetate tetrahydrate. Like the latter it does not melt when heated but appears to desiccate on the bottom of the vessel if heated with its mother liquor. Down the series from lanthanum to dysprosium any desiccated product readily dissolves in the hot solution, and no obvious change results short of actual charring. The earths early in the series soften to a glutinous mass, but gadolinium gives a hard cake. With erbium it appears that decomposition has taken place and a whitish, relatively insoluble, powder remains. This can however be taken up on addition of more water, but the solution then requires to be concentrated before $H_4Na_4Er_4enta_8,24H_2O$ can again be crystallised. The decomposition is only semipermanent; it can be avoided by adequate agitation. The observed facts are consistent with the view put forward later that the fifth enta acid group is held reversibly.

The first fractionation attempted was of the salt prepared from crude gadolinium oxide (300 g.). The material was opened up into nine fractions in six steps. The head fraction then showed no visible absorption bands through 10 cm. of hot concentrated solution. Fraction 2 showed a faint holmium band, which was stronger in fraction 3; these two fractions were faintly greenish with dysprosium. The bulk of the holmium was found in fractions 5 and 6, accompanied by a little erbium. Fraction 9 was poor in holmium but rich in erbium. A similar fractionation with some crude yttrium earths from yttriotungstite, much richer in coloured earths than the above gadolinium oxide, confirmed the rapidity of the separation of dysprosium, holmium, and erbium, and showed that thulium collected at the tail. These

* *J.*, 1950, 1819, and *J.*, 1951, 1461, are now considered to be Parts I and II of this series.

two series were later amalgamated and run with about 25 fractions; a good separation continued to be obtained. The process is more effective than bromate fractionation, but is more bulky, and lack of fusibility of the crystals causes difficulties. Mother-liquors require to be boiled separately from the solids, poured on to them, and then frequently shaken until solution has occurred. The solubility of the salt varies widely with temperature. In a sample of gadolinium it fell from 870 to 20 g. of salt per litre between boiling point and room temperature. The latter amount means that too little material passes down the series in the liquors. The room-temperature solubility of erbium is however considerably greater. Crystals up to 1 cm. diameter have been obtained but are more usually 1—4 mm. in diameter. They are smaller at the head of a series than at the tail, and are of irregular form. Present indications are that use of the salt might be preferred to bromates when only a small amount of material is to be handled, as for instance in the final purification of an element. The most suitable elements for treatment by this method appear to be those in the series from gadolinium to holmium, inclusive. The ease with which the salt can be prepared is a point in its favour. In the course of fractionation a definite acidity arises at the head and alkalinity at the tail. There is evidently a decomposition, and the formula assigned is no longer valid throughout the series. The very rapid initial separation is undoubtedly the result of this decomposition. The solubility, especially in cold solution, increases with complex stability, or $H_4Na_4Ln_4$ enta$_8$ instability. Thus the stronger bases collect in the acid head and the more stable complexes go to the tail. Naturally this separation of acid and base can only proceed to a limited extent. It has been found that at the head (Gd) a pH of about 5·5 (paper test) is the limiting value; at the tail gummy non-crystalline matter soon collects.

The salt has been prepared by three different methods and a 1 : 1 ratio of alkali to lanthanon observed. The amount of enta is generally 1·25 mols. per g.-atom of lanthanon, but it may be less in the yttrium group; in one experiment it appeared to be close to 1·20. Prepared synthetically from 4 mols. of sodium hydroxide, two of gadolinium oxide and five of the acid, the sole product after sufficient boiling was the salt conforming to the formula $H_4Na_4Gd_4enta_8,24H_2O$. By treatment of gadolinium oxide with enta acid and a limited quantity of water, dissolution of the oxide to a neutral solution took rather less acid than that required for the formation of HGd enta. There may therefore have been partial formation of Gd_4enta_8 corresponding to Brintzinger's yttrium salt. Treatment of this solution with 0·5 mol. of N-sodium hydroxide gave a partial precipitation of hydroxide which redissolved with 1 mol. Thus the salt in solution was initially, partly at least, simple but became complex. The solution at this point was strongly alkaline and the solute showed no ability to crystallise. Addition of enta acid to give a total of 1·25 mols. gave a neutral solution from which the solute crystallised well. The following series of reactions are suggested as the main course of the reaction:

$$2Gd_2O_3 \xrightarrow{4H_4enta} 4GdH\ enta \xrightarrow{4NaOH} 4Na[Gd\ enta] \xrightarrow{H_4enta} H_4Na_4Gd_4enta_8$$

In the third method of preparation neutral gadolinium sulphate was treated with neutral trisodium enta. The reaction mixture became acid.

$$Gd_2(SO_4)_3 + 2Na_3H\ enta = 2Na[Gd\ enta] + 2Na_2SO_4 + H_2SO_4$$

Gadolinium oxide was added to maintain neutrality. The complex gadolinium salt and the sodium sulphate were readily crystallised separately; the sodium sulphate exactly accounted for the sulphate originally combined with the gadolinium, but there was a shortage of one atom of sodium for each atom of gadolinium.

It was possible to prepare a soluble neodymium enta salt with at least partial success when neodymium oxide in excess was warmed with enta acid and a little water. The solution showed the characteristically sharpened absorption bands of anionic neodymium (Moeller and Brantley, *J. Amer. Chem. Soc.*, 1950, **72**, 5447). The salt is however unstable to heat, and Brintzinger *et al.* (*loc. cit.*) did not find it in hot dilute solution.

Experimental.

Crude gadolinium oxide from a monazite source was used for most of the synthetical work. It contained about 2% of neodymium oxide, a similar quantiy of dysprosium, and some terbium, but no samarium or europium.

Preparation of the Salt.—Gadolinium oxide (18·1 g., 0·05 mol.) and sodium hydroxide (4·0 g.) in boiling water (about 100 ml.) were treated with H_4enta till all the gadolinium was dissolved and a neutral solution obtained (Required 29 g., 0·125 mol.). The *salt* crystallised fairly completely on cooling, but by evaporation of the mother-liquor a further small crop was obtained; there was a very small quantity of a gummy material. The total yield was 58·8 g. ($H_4Na_4Gd_4enta_8,24H_2O$ requires 58·3 g.).

In a second experiment, to gadolinium oxide (18·1 g.), moistened with a little water and warmed, enta acid was added till dissolution of the gadolinium oxide was complete [Consumed 22·3 g. of enta acid. GdH enta requires 23·6 g. (formation of some Gd_4enta_3 seems indicated)]. The gadolinium passed into solution after going through a glutinous stage. The solution readily formed a glutinous skin on the surface but no crystallisation was observed. To it was added N-sodium hydroxide (50 ml.); this caused some precipitation of hydroxide, but this redissolved when another 50 ml. of the alkali were added, indicating that the original solution contained some simple salt but that a sodium complex had now formed. The solution was now strongly alkaline. To it was added enta acid (6 g.). The pH was then 9; more acid (1 g.) reduced the pH to 3, and a good crop of salt crystallised.

When first encountered the salt was thought to be a sulphato-complex, but this was disproved by the following experiment.

Gadolinium sulphate octahydrate (187 g., 0·25 mol.) was treated with just sufficient M-solution of Na_3H enta (690 ml.) to bring about solution, the neutrality being maintained by addition of gadolinium oxide (13 g.). There was obtained the complex (316 g.), sodium sulphate decahydrate (156 g.), and, on addition of excess of hydrochloric acid to the mother-liquors, sodium chloride (31 g.). No free enta acid was precipitated [Found, corresponding to $Na_2SO_4 + NaCl$; SO_4, 71·7 g.; Na 34·4 g. Input: SO_4, 72 g.; Na, 47·5 g. This corresponds to an input to the complex: Na, 13·1 g.; Gd, 90·1 g.; H_4 enta, 161·8 g.; balance (water), 50·3 g. $H_4Gd_3Na_4enta_4.24H_2O$ requires Na, 13·1 g.; Gd, 89·7 g.; H_4 enta, 161·8 g.; H_2O, 49·4 g.]. This preparation formed about one-third of the material subsequently fractionated.

(b) *Double-sulphate Precipitation from Sodium Lanthanon Enta Solution.*—The solubility of lanthanon alkali sulphates follows the order of increasing complex stability, and the success of the usual process is itself undoubtedly the result of weak complex formation. If therefore a stronger complexing factor is introduced a sharper separation may be expected. The double-sulphate separation of a mixed earth has therefore been studied by both the normal procedure and starting with the complex salt, $H_4Na_4Ln_4enta_4$. The latter procedure gave a much sharper separation of the less soluble earths from the more soluble, but the more soluble salts proved difficult to precipitate at all. However, good recovery of the enta salt is possible because of its low solubility in cold acid solution, if no very heavy earths are present. Double-sulphate precipitation of lanthanon enta solutions is therefore useful chiefly as a means of cleaning small quantities of earths forming the less soluble double sulphates from larger quantities of material giving more soluble double sulphates. Thus it has proved valuable in removing a little neodymium from gadolinium which had been fractionated as double magnesium nitrates, but which, owing to the presence of yttrium, had not proved separable by this means.

For a mixture of earths containing neodymium oxide 2·4%, samarium oxide 13·2%, dysprosium oxide 10%, and much gadolinium a normal double-sulphate precipitation from 10% chloride solution was compared with precipitation from the complex enta solution. From the chloride solution the first 7% of earth to be precipitated contained 6·9% of neodymium oxide and the first 25% averaged 5·6%. Only 30% of the earth was recovered at the tail, free from neodymium. From enta solution the first 20% to be precipitated contained 9·1% of neodymium oxide, and the next 7% carried 1·7%, and left the solution quite free from neodymium.

Double-sulphate precipitation develops an excess of enta in solution, and further precipitation does not then take place. But by the addition of suitable simple lanthanon solution the excess of enta is utilised and further precipitation occurs. The precipitation is also facilitated by sulphuric acid. This will itself, in sufficient quantity, precipitate HLn enta in the cerium group. But if acidification is not carried to this point the salt existing in solution is precipitable more selectively as double sulphate.

$$H_4Na_4Ln_4enta_4 \xrightarrow{H_2SO_4} HLn\ enta \xrightarrow{Na_2SO_4} Ln_2(SO_4)_3.Na_2SO_4$$

Experimental.

Crude gadolinium oxide (25 g.) in solution (300 ml.) as $H_4Na_4Gd_4enta_4$ was treated at the boiling point with sodium sulphate (15 g.), and boiling continued for 30 minutes. The precipitate was collected and more sodium sulphate (15 g.) added as before, without result. Sulphuric acid (2 ml.) was then added; a small precipitate resulted which carried down all the neodymium remaining in solution. Further precipitation on the addition of more acid was unsatisfactory, giving mixed double sulphate and enta salt.

The material used for the fractionation in (*a*) was dissolved in water (4 l.) and sodium sulphate (150 g.) added, and the solution acidified and boiled; a precipitate formed and was collected. No further precipitate formed on boiling the mother-liquors so a solution of an earth chloride mixture was added, having a neodymium content similar to the present content of the reaction mixture. Further precipitation now occurred. The process was repeated by using another chloride solution almost free from neodymium. There thus resulted three nearly equal fractions (43 g. of oxide) having, respectively, 10·3, 5·0, and 1·8% of neodymium oxide. The solution was then quite free from neodymium, and on storage deposited a crystalline complex (750 g.), leaving only a trace of erbium in solution. Previous

work had shown that while the neodymium collected in the head after ten series of crystallisations on ten fractions of the enta$_5$ salt the removal of the last traces of neodymium by this process would not prove outstandingly effective.

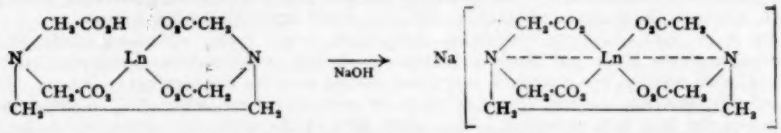
Sometimes double-sulphate precipitation occurred suddenly in an almost colloidal form and showing little selectivity. Such a precipitate redissolved when the solution was made more alkaline and was re-formed with satisfactory results by careful acidification.

The action of a little enta on double-sulphate precipitation was also studied. Sufficient Na_2H enta was added to crude terbium-earth chlorides to give about 25% complex formation. Practically no improvement in the elimination of neodymium or samarium occurred at the start, or indeed before about 75% of the earths had been precipitated, and enta was therefore present in full equivalent. Neodymium was by this time eliminated but samarium separation showed a distinct improvement (1·2% in solid at 85% precipitation as against 4% at 90% precipitation). The concentration of holmium and erbium at the tail was observed to be much improved but the contents were only small and therefore difficult to estimate accurately. The concentration of dysprosium in the fraction, 75—100% precipitation, was improved, the maximum of 25% to 31%. The content in the fraction 45—75% precipitation decreased from an average of 10% to 5%. The practical utility of enta for improving the concentration of earths collecting at the soluble end of a double-sulphate series was not however convincingly demonstrated. The fractional crystallisation of the enta salt appears preferable.

Discussion.

The number of lanthanon and alkali lanthanon enta salts appears to be large and ill-defined. Besides Brintzinger's normal simple salt, HLn enta, the present work has shown the existence of a soluble, unstable, and largely complex, salt for which the formula Ln[Ln enta]$_2$ is suggested corresponding to the supposed alkali complex Na[Ln enta]. Since each [Ln enta] group presents the possibility of *cis-trans* isomerism four isomers are possible of the former salt. The nature of the absorption spectrum makes this formula more likely than an alternative based on the chelate character of the $>N\cdot CH_2\cdot CO_2H$ group in HLn enta. This would give rise to a salt Ln_4enta_3 with only one Ln held in complex combination.

A major point of interest is the extra molecule of H_4enta found in the salt $H_4Na_4Ln_4enta_5$, though it is a mistake to think of it as in any way supernumerary, for it must bind together four [Ln enta] anions. When simple HLn enta is treated with alkali and passes to Na[Ln enta] one electrovalent but two covalent bonds are formed:



An elaborate system of five 5-membered rings comes into existence with hybridised bond orbitals. The result appears to be that the anion, after union with the sodium cation, has a residue of ammoniacal character and can co-ordinate with a hydrogen atom. The co-ordinated amine groups do not here behave as neutral groups as they do with elements which readily form amines. To maintain 6-co-ordination the lanthanon has to accept two amine groups, but the bond is weak and sufficient amine character is left to form a co-ordinate link with hydrogen. The more electropositive the lanthanon the greater is the stability of the enta$_5$ compound. Breakdown of this compound in aqueous solution is not likely to result in liberation of free enta acid but may take the course:

$$Na[Ln\ enta],H_4enta \rightleftharpoons 3HLn\ enta + Na[Ln\ enta] + Na_2H\ enta$$

The phenomena already described appear to be satisfactorily accounted for on this hypothesis, if solid solution is easily formed between the various components of the system. HLn enta is only slightly soluble but Na[Ln enta] and Na_2H enta are highly soluble in water. If therefore a mixture of the above components but mainly enta$_5$ salt is crystallised the head crystals will be rich in HLn enta and the tail in Na[Ln enta]. At the same time a separation according to basic strength is brought about, the strong bases preferring the simple salt form and the weak bases the complex.

Fractionation by this process therefore depends upon instability of the 5-enta salt. In practice it has been found that the cerium earth salts are too stable to be worked satisfactorily. A concentration of the ytterbium earths in an uncrystallisable tail is rapidly obtained. The earths Gd, Tb, Dy, and Ho appear to be those which respond best to treatment.

The Dyson Perrins Laboratory, Oxford. [*Received, June 14th*, 1951.]

677. *The Nature of the Co-ordinate Link. Part IV.* Complex Formation by Phosphorus Trifluoride.*

By J. Chatt and A. A. Williams.

It is considered that the *trans* influence of certain ligands, notably ethylene, carbon monoxide, the nitro-group, and to a lesser extent trialkylphosphines, in platinous complexes, is due to a mechanism of co-ordination involving in some special manner electrons from *d*-orbitals of the metal, and consequently that phosphorus trifluoride, where the strongly electronegative fluorine should enhance this effect as compared with the trialkylphosphines, should show considerable resemblance to carbon monoxide in its complexes.

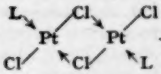
This was confirmed; with boron trifluoride and aluminium salts where *d*-electrons are not available, no complex formation takes place, but with platinous chloride were obtained two uniquely volatile stable compounds, $(PF_3)_2PtCl_2$ and $(PF_3,PtCl_2)_2$, very similar to the corresponding carbonyl complexes. It was shown that either the mononuclear carbonyl and phosphorus trifluoride compounds have a *cis*-configuration or that their benzene solutions contain an exceptionally high proportion of the *cis*-isomer in equilibrium with the *trans*-compound, by dipole-moment measurement. With aurous and cuprous chlorides, phosphorus trifluoride behaves very much as does carbon monoxide, also it replaces carbon monoxide from nickel carbonyl without altering the character of the complex. It is suggested that there are two methods of co-ordination: (1) the classical co-ordinate link; and (2) a method of bonding also involving in some special manner *d*-electrons in the metal atom. The second method is essential for stable complex formation by carbon monoxide, ethylene, phosphorus trifluoride, and such ligands. Whether (2) is partial double bonding, the most obvious explanation, is still an open question. The bond (2) appears to be much less polar than (1), and to require for its formation the presence of vacant or potentially vacant orbitals in the donor atom as well as filled *d*-orbitals in the metal atom.

In a previous communication it was suggested that filled *d*-orbitals in a metal atom played a much more important part in general co-ordination than had hitherto been supposed, particularly that in the co-ordination of olefins to give covalent complex compounds, as in their co-ordination to platinous salts, the presence of filled *d*-orbitals on an energy level close to that of the outer shell *s*- and *p*-orbitals appears to be absolutely essential (Chatt, *J.*, 1949, 3340).

trans *Influence and the Use of* d-*electrons in Co-ordination to Platinum*(II).—Olefin complexes are not unique amongst platinous complexes; although their properties are somewhat different from those of the platinous ammines, they resemble closely those of the analogous carbonyl compounds. This correspondence has been noted by most recent workers in this field (*e.g.*, Anderson, *J.*, 1934, 972), and in looking for a quantitative measure of this similarity it seemed that *trans* influence could be used. Chernyaev (*Ann. Inst. platine, U.R.S.S.*, 1926, **4**, 261) established that certain groups [*e.g.*, $-NO_2$, $-CN$, $SC(NH_2)_2$] attached to platinum in platinous complexes produce considerable labilisation of the group in the *trans*-position to themselves, so that the *trans*-group is most easily eliminated during chemical reactions. The greater the *trans* influence the greater the labilising effect and the ease of elimination of the *trans*-substituent. The order of *trans* influence of various groups has been established only qualitatively, but ethylene and carbon monoxide show it to a marked degree (Hel'man, "Complex Compounds of Platinum with Unsaturated Molecules," *Soviet Acad. Sci.*, 1945; see also Chatt, *Ann. Reports*, 1946, **43**, 120), whereas ammonia and water have no appreciable effect. The effect is also displayed by the tertiary phosphines and organic sulphides, but in our experience the *trans* influence of tri-*n*-propylphosphine is inferior to that of ethylene. Tri-*n*-propylphosphine has a greater *trans* influence than *p*-toluidine and ammonia because *trans*-$[C_2H_4,NH_2,PtCl_2]$ and *trans*-$[C_2H_4,p\text{-}C_7H_7\cdot NH_2,PtCl_2]$ are stable compounds, whereas *trans*-$[C_2H_4,Pr^n_3P,PtCl_2]$ loses part of its ethylene at room temperature and has never been isolated (Chatt, *J.*, 1951, 652). This latter fact may suggest that tri-*n*-propylphosphine has a greater *trans* influence

* Part III, *J.*, 1951, 2532.

than ethylene because it is the ethylene which is eliminated, but it must be remembered that in any circumstances ethylene is only weakly bound to platinum, whereas the trialkylphosphines are amongst the more strongly bound ligands. Ethylene has in fact a much greater *trans* influence than tri-*n*-propylphosphine, a measure of which is provided by the stability of the halogen bridges in the bridged complexes, type (I). These complexes have normal molecular weights in boiling benzene but dissociate reversibly in boiling acetone, doubtless because the chlorine of the bridge is replaced by acetone in the same way, but to a much less extent than was shown to occur in the platinic series (Chatt, *J.*, 1950, 2301).



(I) $+ 2Me_2CO \rightleftharpoons 2Me_2CO,L,PtCl_2$ (L = ligand)

We find that when L is tripropylphosphine dissociation occurs to the extent of only *ca.* 45% as compared with *ca.* 70% when L is ethylene, both solutes at 0·03M. concentration. With sufficiently accurate molecular-weight determinations, this dissociation should provide a direct method for the assessment of bridge stability and of *trans* influence over the important range covered by the tertiary phosphines and similar molecules. We are attempting to make these measurements, but record this preliminary result because Syrkin (*Bull. Acad. Sci., U.R.S.S., Classe sci. chim.*, 1948, 69) considers alkylphosphines to show the greatest *trans* influence. He quotes no experimental evidence of this, but it is an important point in his hypothesis of *trans* influence.

Qualitatively, from numerous papers from Chernyaev's pupils, it appears that the best arrangement, in order of increasing *trans* influence, for a number of common ligands, is $H_2O < OH < NH_3 \sim F < Cl < Br < I \sim R_3P \sim R_2S < SC(NH_2)_2 < NO_2 < CO \sim C_2H_4 < CN$.

It appears significant that those groups showing greatest *trans* influence are those which combine only weakly with the salts of aluminium, magnesium, and other elements having no *d*-electrons. On the other hand, those near the beginning of the above series combine most strongly with the lighter group 2 and 3 elements but not markedly with the transition metals and others which have *d*-electrons. Also those groups showing highest *trans* influence are those which Pauling considered to co-ordinate by double bonds making use of filled *d*-orbitals of the metal atom for π-bond formation (" Nature of the Chemical Bond," pp. 231—238, Cornell, Univ. Press, 1939; see also Syrkin and Dyatkina, *Acta Physicochemica, U.R.S.S.*, 1945, **20**, 137, 273; " Structure of Molecules," English Translation, p. 358—393, Butterworths).

Syrkin and Dyatkina also consider that double bonding, P=Pt, contributes to the strength of binding in the trialkylphosphine series of platinous complexes (*J. Gen. Chem. U.S.S.R.*, 1946, **16**, 345; *Bull. Acad. Sci. U.R.S.S., Classe sci. chim.*, 1948, 75). Calvin and Melchior (*J. Amer. Chem. Soc.*, 1948, **70**, 3270) in their study of chelate copper complexes also consider *d*-orbitals to contribute to the stability of suitably substituted chelate rings. We think that bonding which requires the use of the *d*-electrons in some special manner, perhaps in π-bonding, is the cause of *trans* influence; and the qualitative experiments with phosphorus trifluoride as ligand had the object of testing this idea.

It should be noted that Grinberg (*Chem. Abs.*, 1945, **39**, 252) has suggested an exactly opposite explanation of *trans* influence. He suggested that the weakening of the bond *trans* to the groups of high *trans* influence is due to the mobility (or polarizability) of electrons in these groups, and the ease with which they move towards the platinum atom. Our results are completely opposed to this idea.

It is obvious that if *trans* influence is due to the use of one or more filled *d*-orbitals in the platinum atom to bind by π-bonding the donor atom, then replacement of the alkyl groups in trialkylphosphines (R_3P) by more electronegative groups, thus increasing the drift of electrons in the *d*-orbitals towards the phosphorus atom, should cause the phosphines to be placed increasingly nearer to the right in the above *trans*-influence series as electronegativity of R is increased. We chose fluorine atoms as extremely electronegative groups, and hoped to find that phosphorus trifluoride would lie so far along the *trans*-influence series that its complexes would be very similar to those of carbon monoxide. This prediction was amply confirmed (see also Chatt, *Nature*, 1950, **165**, 637).

The Co-ordination Chemistry of Phosphorus Trifluoride.—Phosphorus trifluoride complexes with metallic salts do not appear to be known, except that Moissan (*Bull. Soc. chim.*, 1891, [3], **5**, 454) obtained a substance F_3PPt, by reaction of phosphorus pentafluoride with spongy platinum, considered to be analogous to Schützenberger's $PCl_3,PtCl_2$ (*ibid.*, 1872, **17**, 482) which must be dimeric.

When phosphorus trifluoride was passed through a plug of powdered platinous chloride at 200—220°, two substances immediately started to sublime into the colder part of the tube. With phosphorus trifluoride in excess, there was obtained bis(trifluorophosphine)dichloroplatinum, $(PF_3)_2PtCl_2$, which we shall call the dichloride, in colourless crystals melting to a very pale yellow liquid at 102°. In a slow stream of the gas were obtained orange yellow crystals of composition PF_3PtCl_2, doubtless dimeric dichlorobis(trifluorophosphine)-μμ′-dichlorodiplatinum with the structure (I; L = PF_3), which we shall call the tetrachloride, together with the dichloride which is considerably more volatile. The tetrachloride melts to a red liquid at 155—156°. These complexes closely resemble the corresponding carbonyl platinous halides which were hitherto the most volatile platinous complexes known. The phosphorus trifluoride complexes are, however, more stable and more volatile. The dichloride can be boiled under reflux at atmospheric pressure at about 240° but loses phosphorus trifluoride rapidly, passing into the tetrachloride with consequent rise in boiling point until at 285° decomposition with gradual separation of solid occurs. The tetrachloride can be distilled completely at 15—20 mm. pressure without any decomposition.

The P–F bond is unfortunately too easily hydrolysed to allow of a thorough study of the chemical properties of the chlorides. They dissolve in water to give clear solutions (colourless and orange-yellow, respectively) in which the platinum is so firmly bound that it cannot be precipitated from acid solution by metallic magnesium. These solutions probably contain the phosphorus acid derivatives described by Schützenberger (*ibid.*, 1872, **17**, 482) and were not further examined. This hydrolysis has of course, no parallel in the carbonyl platinous halide series where another type of hydrolysis occurs with liberation of platinum (Schützenberger, *ibid.*, 1870, **14**, 17):

$$(CO)_2Pt_2Cl_4 + 2H_2O = 2CO_2 + 2Pt + 4HCl$$

The white simple complex compounds, $(PF_3)_2PtCl_2$ and $(CO)_2PtCl_2$, are less soluble in benzene and carbon tetrachloride than the corresponding bridged compounds, $(PF_2PtCl_2)_2$ and $(COPtCl_2)_2$. These observations suggested that they have *cis*-configurations which were supported by the approximate values = 4·4 D and = 4·65 D, respectively, found for their dipole moments (1 D = 10^{-18} e.s.u.). When we consider that the Ni–Br bond appears to have a moment of about 2·5 D (Jensen and Nygaard, *Acta Chem. Scand.*, 1949, **3**, 476), the greater part of these moments would be accounted for by the Pt–Cl bonds, and if they are the true moments of these molecules then the F_3P–Pt and OC–Pt groupings must be almost non polar.

The value 4·4 D is also to be contrasted with the values of the order 11 D found by Jensen for *cis*-bis(trialkylphosphine)dichloroplatinums (*Z. anorg. Chem.*, 1936, **229**, 250). This great difference cannot be explained by the simple replacement of the alkyl groups by fluorine, which would lower the dipole moment by about 2—3 D so we would expect a moment of about 8—9 D for *cis*-$(PF_3)_2PtCl_2$ if the P–Pt link is the same as that in alkylphosphine-platinous complexes. Thus it appears that there is a large neutralisation of the Pt–P co-ordinate link by the opposing drift of *d*-electrons in the phosphorus trifluoride complexes. It is interesting too that the carbonyl and phosphorus trifluoride complexes have moments so closely similar.

However, the dipole moments could also be explained if we suppose that the solid *cis*-complexes isomerise spontaneously, and immediately in solution, to an equilibrium mixture of the *cis*- and the *trans*-isomers. We have no evidence of this occurring, but even if it does occur and the moment of pure *cis*-$(PF_3)_2PtCl_2$ is 8—9 D the equilibrium mixture must contain about 30% of *cis*-isomer. This is ten times the quantity of *cis*-$(PPr_3)_2PtCl_2$ observed for the same equilibrium in the tri-*n*-propylphosphine series and three times that in the triethylphosphine series (Chatt and Wilkins, Part V, unpublished).

Either of the above explanations shows that the stability of the *cis*-isomer relative to the *trans*-compound has been greatly increased by replacing alkyl groups by fluorine atoms. This fact is significant for the view that *d*-orbitals in the platinum atom take part in co-ordination, because *d*-orbitals are in planes at right angles to each other (see Coulson, *Quart. Reviews*, 1947, **1**, 146). In whatever manner they are used in the binding, it is only in the *cis*-isomer that different *d*-orbitals are available to bind each molecule of the phosphine. In the *trans*-isomer the same *d*-orbitals would have to bind both phosphorus atoms to the platinum atom leading to weaker binding. The observed greater stability of the *cis*-isomer is thus good evidence that *d*-orbitals play a more significant part in binding phosphorus trifluoride than in the binding of alkyl phosphines to platinum.

With cuprous and aurous chloride, phosphorus trifluoride behaved qualitatively in a similar manner to carbon monoxide, but the complexes appeared slightly less stable; they were too

unstable for analysis. We obtained no complex with palladous chloride. The only carbonyl, $(CO)_2Pd_2Cl_4$, is known to be very unstable (Manchot and König, *Ber.*, 1926, **59**, 883).

Attempt to prepare $Ni(PF_3)_4$.—It was expected that this compound would be volatile and similar to nickel carbonyl, but attempts to combine phosphorus trifluoride with freshly reduced nickel at atmospheric pressure and in sealed Carius tubes at pressures up to the bursting point at 100° for 6 hours gave no evidence of combination (cf. Mond, *J.*, 1890, **57**, 749). Nor would phosphorus trifluoride replace carbon monoxide from nickel carbonyl at room temperature. By recycling nickel carbonyl (b. p. 43°; 100 c.c.) with phosphorus trifluoride through a heated tube for 100 hours, fractions boiling up to 68° were obtained. The high-boiling fractions from a number of experiments analysed in the range $(CO)_2Ni(PF_3)_2$—$(CO)Ni(PF_3)_3$, and were liquids even at −78°. As considerable decomposition to metallic nickel occurred in the hot tube during the initial stages of the experiment, but not towards the end, the substituted nickel carbonyl is obviously more stable than nickel carbonyl itself. Nevertheless, because of its higher boiling point, considerable decomposition occurred during the fractionation of the product, and a pure fraction was not isolated. Although most donor substances, *e.g.* pyridine and triphenylphosphine, can replace two molecules of carbon monoxide from nickel carbonyl to yield solid derivatives, it was now obvious that phosphorus trifluoride can replace more than two, without producing a change in the character of the complex.

This partial replacement has an exact parallel in the replacement of carbon monoxide by cyanide ion. Although $K_4Ni(CN)_4$ can be obtained by reduction of $K_2Ni(CN)_4$ with potassium (Eastes and Burgess, *J. Amer. Chem. Soc.*, 1942, **64**, 1187) attempts at direct replacement lead to a mixture with maximum replacement of only three carbon monoxide molecules (Burg and Dayton, *J. Amer. Chem. Soc.*, 1949, **71**, 3233). Hieber (*Z. Naturforsch.*, 1950, **5***b*, 129) also finds that only three molecules of carbon monoxide can be replaced directly by methyl *iso*cyanide, but $Ni(MeNC)_4$ was obtained indirectly. The increasing stability as carbon monoxide is replaced by phosphorus trifluoride indicated that $Ni(PF_3)_4$ would probably be obtained by a suitable indirect method. At this stage of the research, we learned that J. W. Irvine and G. Wilkinson of the Massachusetts Institute of Technology had prepared $Ni(PCl_3)_4$, a non-volatile solid (personal communication, to be published in *Science*, 1951), and later that Wilkinson had obtained $Ni(PF_3)_4$ from this chloride by reaction with antimony trifluoride and also by replacement of the phosphorus trichloride by phosphorus trifluoride under pressure (personal communication). It is a liquid, boiling without decomposition at 71° and melting at −54°. The analogy between phosphorus trifluoride and carbon monoxide in their behaviour with the transition metals and salts thus appears to be extremely close.

If co-ordination occurs only by the classical co-ordinate link we would not expect phosphorus trifluoride to form stable complexes because the tendency to donate the lone pair will be greatly reduced by the inductive effect of the fluorine atoms. We therefore attempted to prepare complexes with aluminium chloride and with aluminium bromide. Here there are no filled *d*-orbitals in the metal atom and no complex formation took place either when phosphorus trifluoride was passed over heated aluminium chloride or through a solution of aluminium bromide in *cyclo*hexane. Boron trifluoride is one of the strongest acceptor molecules known, yet Booth and Walkup (*J. Amer. Chem. Soc.*, 1943, **65**, 2334) showed that no combination whatsoever took place between it and phosphorus trifluoride at temperatures down to the freezing points of mixtures of the gases. Here phosphorus trifluoride is behaving similarly to ethylene, which forms its most stable complexes with platinous chloride, yet shows no association whatsoever with trimethylborine (Chatt, *J.*, 1949, 3343).

Phosphorus trichloride is closely similar in behaviour to phosphorus trifluoride, but, because of the more electropositive character of chlorine as compared with fluorine, the lone pair in phosphorus trichloride is not so inert, and an unstable complex BF_3,PCl_3, decomposing at −6°, has been described (Baumgarten and Bruns, *Ber.*, 1947, **80**, 517). The well-known complexes with platinous chloride, $(PCl_3)_2PtCl_2$ and $(PCl_3)_2Pt_2Cl_4$, are formed at 250° and, like the fluoro-complexes, have considerable thermal stability (Schützenberger, *Bull. Soc. chim.*, 1872, **17**, 482); also Jensen (*Z. anorg. Chem.*, 1937, **231**, 365) concludes from dipole-moment measurements that $(PCl_3)_2PtCl_2$ has a *cis*-configuration.

We are thus left with little doubt that the use of filled *d*-orbitals is essential for stable complex formation by ligands such as phosphorus trifluoride, carbon monoxide, ethylene, etc., which have a high *trans* influence, and that platinum probably owes its unique complex chemistry to a mechanism of co-ordination in which the use of filled *d*-orbitals is essential. There appear to be two distinct methods of co-ordination: (1) by the classical co-ordinate link, covalent or ion dipole, used in complex formation by compounds of boron, aluminium, magnesium,

etc., and (2) by a mechanism, essentially covalent, involving also filled *d*-orbitals of the acceptor atom. The second mechanism leads to a much less polar link than the first and is displayed particularly by platinous salts and complexes in which the metals display zero valency, but to a lesser extent by other metals having filled *d*-orbitals. It is also most marked when these metals are in a low valency state or in the last complete series of the Periodic Table, presumably because electrons from *d*-orbitals are then most readily available.

This second mechanism, which appears to be related to *trans* influence, is easiest visualised as double bonding, but its nature is still an open question. The original evidence for double bonding in the carbonyls and such complexes, based on short metal–ligand bond distances, has been severely criticised by Wells (*J.*, 1949, 55). In the carbonyl complexes, a double metal–carbon bond requires that the C–O bond should also be double, and in the metal carbonyls the C–O bond length (1·15 Å) which is only slightly altered from that in carbon monoxide (1·13 Å) (Sheline, *J. Amer. Chem. Soc.*, 1950, **72**, 5761), is very close to that in keten (1·17 Å) (Beach and Stevenson, *J. Chem. Phys.*, 1938, **6**, 75; see also, Long and Walsh, *Trans. Faraday Soc.*, 1947, **43**, 342); also those ligands which show greatest *trans* influence are those that have vacant orbitals, *e.g.*, the 3*d* in phosphorus trifluoride, or potentially vacant orbitals, *e.g.*, 2*p* in the nitro-group and carbon monoxide, and which could be used for π-bond formation with a filled *d*-orbital of the metal atom.* The chemistry of platinum complexes accords with this view, only if such π bonding also leads to a marked weakening of the σ bond in the *trans*-position, because all groups, even amines where no similar N–Pt double bond is possible, are subject to *trans* influence by the carbon monoxide type of ligand. The behaviour of phosphorus trifluoride as a ligand also rules out any suggestion that *trans* influence is a purely inductive effect, because the inductive effect of the fluorine atoms should lead to an increase in the strength of attachment of the other three ligands to the platinum, not to a decrease, in the attachment of the *trans*-ligand. Work is continuing to establish with more certainty whether or not the second method of co-ordination is in fact by double bonding.

Experimental.

Dissociation of Chlorine-bridged Platinous Complexes in boiling Acetone.—The apparent molecular weights of dichlorobis(tri-*n*-propylphosphine)-μμ′-dichlorodiplatinum and dichlorodiethylene-μμ′-dichlorodiplatinum (I; L = Pr_3P and I; L = C_2H_4) were determined by using a semimicro Swietoslawski apparatus (5 c.c.). The accuracy is only sufficient to give the order of the dissociation constant (*K*), but leaves no doubt that the ethylene complex is much more dissociated than the propylphosphine complex. Unchanged materials were recovered from the acetone solutions, thus proving that the dissociation does not occur at the metal–ligand bond. If this had occurred ethylene would have been lost rapidly from the boiling solution with deposition of insoluble platinous chloride and an apparently very large molecular weight would have been found.

$(Pr_3PPtCl_2)_2$; M = 853.

Molar concn.	Apparent M	% dissocn.	10^3K
0·0157	555	53·8	3·9
0·0268	571	49·4	5·2
0·0306	591	44·3	4·35
0·0316	591	44·3	4·5
		Average	4·5

$(C_2H_4PtCl_2)_2$; M = 588.

Molar concn.	Apparent M	% dissocn.	10^3K
0·0168	340	73·0	13·3
0·0285	337	74·5	24·7
0·0345	357	65·1	16·7
0·0482	353	66·6	25·6
		Average	20

Preparation of Phosphorus Trifluoride.—Zinc fluoride was dried at 140—150° for at least 12 hours, and phosphorus trichloride dropped (1 drop in 3 seconds) on to the dry powder (50—60 g.). There was an induction period of about 5 minutes, and care was necessary not to flood the zinc fluoride or the reaction may not start. When the reaction had started it was controlled by ice cooling, and the rate of flow of phosphorus trifluoride by the rate of addition of the trichloride. Finally it was necessary to warm the mixture to complete the reaction. About 40 c.c. of phosphorus trichloride were required and a brisk stream of the trifluoride was evolved for 1½ to 2 hours. We found it best to work on this scale, and if a faster stream of trifluoride is required, to run a number of preparations in parallel. Zinc fluoride was used rather than the more usual arsenic trifluoride because it is commercially available. The trifluoride was passed through two traps cooled in solid CO_2–acetone and a sulphuric acid bubbler before use.

Preparation of Bis(trifluorophosphine)dichloroplatinum, $(PF_3)_2PtCl_2$ (*Dichloride*).—Powdered platinous chloride (0·7 g.) was loosely packed between asbestos plugs in a Pyrex tube (*ca.* 6 mm. bore) and warmed in a stream of dry nitrogen to remove all moisture. The nitrogen was then replaced by phosphorus trifluoride and the temperature raised to 200—220°. Orange and white crystals sublimed into the

* [*Added, Oct. 1st*, 1951.] The necessity for vacant orbitals is well illustrated by Wilkinson's observation (*Nature*, 1951, **168**, 514) that PF_3, but not NF_3, combines with hæmoglobin in a manner similar to that in which CO combines. The inertness of NF_3 to hæmoglobin is attributed to the absence of 2*d*-orbitals.

cooler part of the tube, and, when all the platinous chloride had reacted leaving only a small black residue, the sublimate was resublimed in an excess of phosphorus trifluoride into a part of the tube between two constrictions where the *dichloride* condensed in pure white crystals. The tube was allowed to cool, the phosphorus trifluoride driven out by dry nitrogen, and the part of the tube containing the product (0·72 g.) sealed off at both ends to prevent ingress of moisture. This had m. p. 102°, melting to a faintly yellow liquid which reddened on further heating until it boiled at 240° in dry nitrogen at atmospheric pressure. There was rapid loss of phosphorus trifluoride. As boiling continued, the temperature gradually rose to 285° at which temperature decomposition with deposition of dark-coloured solids was also occurring (Found : Cl, 16·1; Pt, 43·9. $Cl_2F_4P_2Pt$ requires Cl, 16·0; Pt, 44·15%). The dichloride is slightly soluble in dry benzene, and hydrolyses rapidly in air to give a deliquescent substance. Platinum could not be precipitated from the solution in water by magnesium metal, but chlorine was estimated gravimetrically. In the determination of platinum the solution was oxidised by boiling it with a few c.c. of aqua regia, taken to dryness twice with 20% hydrochloric acid, and platinum precipitated with magnesium.

Preparation of Dichlorobis(trifluorophosphine)-μμ′-dichlorodiplatinum, $(PF_3)_2Pt_2Cl_4$ (*Tetrachloride*).—The mixed sublimate obtained as in the previous preparation was collected in a U-tube containing platinous chloride (0·8 g.), and the gaseous phosphorus trifluoride replaced by dry nitrogen. The solid was then melted on to the platinous chloride, and the liquid maintained at just above its freezing point for 3 hours; this necessitated a gradual rise in temperature. Any white solid subliming was melted and run back into contact with the platinous chloride. The tube was then sealed half-way down the limb from which the sublimate had entered, and the liquid gently refluxed with the platinous chloride at 100 mm. pressure until no further reddening of the liquid occurred (15—30 minutes). The red substance was now sublimed from the platinous chloride at 15 mm. pressure, and the orange-red *tetrachloride* separated from the residual more volatile dichloride by repeated fractional sublimation at 15—20 mm. pressure. It had m. p. 155—156°, b. p. *ca.* 290° (decomp.) (yield 1·1 g.) (Found : Cl, 19·4; Pt, 55·5. $Cl_4F_6P_2Pt_2$ requires Cl, 20·0; Pt, 55·1%). In air it deliquesced to a yellow solution.

Dipole Moments of $(PF_3)_2PtCl_2$ *and* $(CO)_2PtCl_2$ *in Benzene.*—These were determined by using a heterodyne beat apparatus based on that of Hill and Sutton (see *J.*, 1949, 2313) in a rhodium-plated cell identical with that described by Jenkins and Sutton (*J.*, 1935, 609). Owing to the low solubility and marked sensitivity to moisture of these materials only approximate moments, sufficiently accurate for our present purpose, were obtained from the dielectric-constant (ε) measurements. An allowance of 10% of the total molar polarisation (P_m) was made for the electron (P_e) and atom polarisations (P_a) (cf. Jensen, *Z. anorg. Chem.*, 1935, 225, 109). Moments were calculated by using the formulæ (cf. Jensen, *Acta. Chem. Scand.*, 1949, **3**, 479) :

$$P_m - P_a - P_e = 90\%\ P_m = \frac{900}{C}\left[\frac{\varepsilon_{soln.}-1}{\varepsilon_{soln.}+2} - \frac{\varepsilon_s-1}{\varepsilon_s+2}\right]$$

$$\mu = 0{\cdot}01273\sqrt{(P_m - P_a - P_e)T}$$

Measurements were made at 25°. The dielectric constant of pure benzene (ε_s) was assumed to be 2·273.

	Molar concn.	$\varepsilon_{soln.}$	P_m	μ
$(PF_3)_2PtCl_2$	0·004697	2·285	426	
	0·004868	2·287	472·5	
	0·010743	2·3025	448	4·4 ± 0·5
$(CO)_2PtCl_2$	0·004647	2·287	491	
	0·006097	2·292	508·5	4·65 ± 0·5

Reaction of Phosphorus Trifluoride with Cuprous Chloride.—Attempts to cause cuprous chloride to react with phosphorus trifluoride in the same way as platinous chloride at temperatures up to 340° were unsuccessful. Phosphorus trifluoride was passed through a suspension of cuprous chloride in dry chloroform; a slow reaction took place with formation of a brown solution, which was decanted from unreacted cuprous chloride, and warmed slightly; it became colourless with evolution of phosphorus trifluoride and separation of cuprous chloride. No complex was isolated (cf. Kharasch and Isbell, *J. Amer. Chem. Soc.*, 1930, **52**, 2918, for the corresponding behaviour of carbon monoxide).

Reaction of Phosphorus Trifluoride with Aurous Chloride.—When phosphorus trifluoride was passed through a mixture of auric and aurous chloride at temperatures up to 150°, reduction to metallic gold was the main reaction, but at *ca.* 120° a small quantity of white volatile solid was obtained; it was too unstable for analysis. Pure aurous chloride behaved similarly, the volatile solid being obtained at 110°. Kharasch and Isbell (*loc. cit.*) also noted that carbon monoxide reacted only over a short temperature range about 110°.

When phosphorus trifluoride was passed through a benzene suspension of aurous chloride, a colourless solution was obtained which, on evaporation to dryness at 15 mm. pressure, deposited a white solid. This solid was sensitive to moisture and gradually deposited metallic gold, but is doubtless analogous to COAuCl similarly obtained by Kharasch and Isbell (*loc. cit.*).

Attempt to combine Phosphorus Trifluoride with Freshly-reduced Nickel.—Nickel monoxide (1 g.) in a Carius tube was reduced with hydrogen at 400° and the tube evacuated to 10^{-4} mm. pressure. Phosphorus trifluoride gas (2 l.) was condensed into the tube, which was then sealed and heated to 100° for 6 hours (pressure *ca.* 35 atmos.). When the tube was cold the gases were frozen (liquid nitrogen), the tube opened, and the gases escaping as it warmed were passed through a glass tube at 400°. These contained no volatile nickel compound as was evident from the absence of a nickel mirror or other stain on the hot glass. No liquid remained in the Carius tube and the nickel showed no sign of any reaction.

Reaction of Phosphorus Trifluoride with Nickel Carbonyl.—Phosphorus trifluoride was passed through nickel carbonyl (100 c.c.) at 40°, then through an Liebig condenser with an 18″ steam-heated jacket.

The vapours were condensed (solid CO_2–acetone trap), and the condensed product returned to the nickel carbonyl bubbler every 6 hours. The rate of flow was such that about half the carbonyl was carried through in that time. Some nickel was deposited as the vapours entered the hot condenser, but after *ca.* 70 hours this decomposition ceased. The product, which condensed to a solid during the early part of the experiment, now condensed as a liquid. After 100 hours, 65 c.c. of liquid (Ni, 17·7%) remained. This was fractionated, a modified Podbielniak still being used, but considerable decomposition occurred and no definite fractions were obtained. The highest-boiling fraction (3—4 c.c.), b. p. 66—67°, was analysed (Found: Ni, 16·3, 16·2. COF_4P_2Ni requires 16·75%). The analysis thus corresponds to the replacement of three molecules of carbon monoxide, but we have no evidence from the boiling-point curve that this is a pure *substance*. Many similar experiments were tried without getting greater replacement.

Attempt to Combine Phosphorus Trifluoride with Aluminium Halides.—Phosphorus trifluoride was passed over freshly sublimed aluminium chloride at temperatures up to 250°. No evidence of combination was obtained and the sublimate, thus obtained in a stream of phosphorus trifluoride, contained no phosphorus. Aluminium bromide, obtained by cautious addition of bromine to aluminium turnings, was dissolved in dry *cyclo*hexane and phosphorus trifluoride passed through. No precipitate or evidence of combination was obtained, although other donor substances, *e.g.* dry pyridine, gave an immediate precipitate with such a solution.

The authors gratefully acknowledge useful discussion with Dr. R. S. Nyholm and Dr. D. P. Craig, the considerable help received from Dr. L. E. Sutton, F.R.S., Mr. S. T. Lunt, and Mr. H. R. J. Robins, in designing and building the dipole-moment apparatus, and also The Mond Nickel Company for a gift of nickel carbonyl.

Imperial Chemical Industries Limited, Butterwick Research Laboratories,
The Frythe, Welwyn, Herts. [*Received, July 11th*, 1951.]

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678. *Simple Analogues of Cortisone. Part I. Some Monocyclic Compounds.*

By J. D. Billimoria and N. F. Maclagan.

1-Acetoxyacetyl*cyclo*hexanol, the parent ketol, and 1-hydroxyacetyl*cyclo*pentanol have been prepared by reaction of 1-hydroxy*cyclo*hexane- and 1-hydroxy*cyclo*pentane-1-carboxylic acid, respectively, with methyl-lithium and subjection of the resulting ketones to halogenation and acetolysis or hydrolysis. Ethyl phenylglyoxylate and ethyl 1-hydroxy*cyclo*hexylchloroacetate were also examined as starting materials for the preparation of 1-hydroxyacetyl*cyclo*hexanol and the corresponding triol but were found unsuitable.

The preparation of simple alicyclic compounds containing the dihydroxy-keto-grouping characteristic of cortisone as in (I) and the corresponding triol (II) was undertaken to see if such compounds possessed useful biological activity.

(I) HO·X·CO·CH_2·OH HO·X·CH(OH)·CH_2·OH (II) (X = alicyclic)

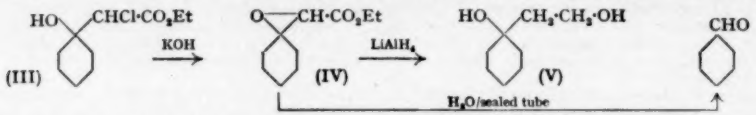
During our present investigations, Wagner and Moore (*J. Amer. Chem. Soc.*, 1950, **72**, 1874) published an account of a preparation of 1-hydroxyacetyl*cyclo*hexanol. Following a totally different route, we have been able to prepare the monoacetate of this compound, the free ketol in higher yields, and also 1-hydroxyacetyl*cyclo*pentanol (cf. Billimoria and Maclagan, *Nature*, 1951, **167**, 81).

In a preliminary attempt to synthesise the triol (II; X = C_6H_{10}) the hydrogenation of ethyl phenylglyoxalate was studied. However, a product was obtained which had the composition $C_{10}H_{14}O_3$; lithium aluminium hydride reduction of this yielded a compound $C_9H_{12}O_2$, whereas oxidation with alkaline potassium permanganate gave an unidentified acid, m. p. 136—137°, and further experiments on this line were therefore abandoned.

The chloro-ester (III) (Darzens and Lévy, *Compt. rend.*, 1937, **204**, 272) was converted quantitatively into the epoxide (IV); fission of this which might have furnished a diol ester led, however, to undesirable products. The epoxide (IV) was recovered unchanged on treatment with dilute mineral acids whilst heating it with water at 180° resulted in the isolation of *cyclo*hexanealdehyde.

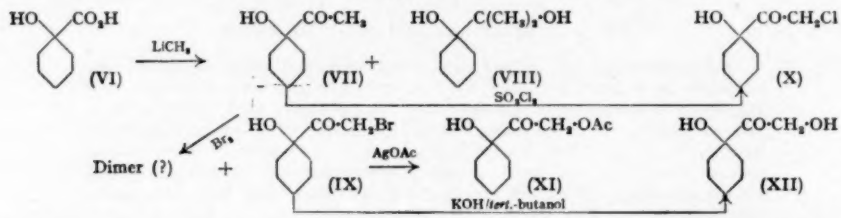
With the object of replacing the halogen atom by an acetoxy-radical, (III) was heated with silver acetate in acetic acid; the unexpected product may be the 1-acetoxy-chloro-ester.

Reduction of (IV) by means of lithium aluminium hydride resulted in the formation of 2-1′-hydroxy*cyclo*hexylethanol (V). The alternative αβ-diol structure was unlikely as the compound did not react with benzaldehyde or acetone. Selective reduction of the ester group in (IV) by use of 0·5 mol. of lithium aluminium hydride gave the same compound and some unchanged epoxide.



Ultimately, 1-hydroxy*cyclo*hexane-1-carboxylic acid (VI) proved to be a more useful intermediate. The acid when treated with ethereal methyl-lithium gave a mixture of acetyl-*cyclo*hexanol (VII), and 2-1′-hydroxy*cyclo*hexylpropan-2-ol (VIII); under selected experimental conditions, the formation of the alcohol could be almost eliminated and the desired ketone obtained in 73% yield.

Attempts to brominate the hydroxy-ketone (VII) with *N*-bromosuccinimide failed completely and bromine itself ultimately proved satisfactory. Bromination of (VII) in chloroform in the presence of calcium carbonate was slow and incomplete; when bases such as pyridine or sodium acetate were used there was no bromination even at 100°. Rapid absorption of bromine took place, however, at 40° when light petroleum was used as solvent, the product being a readily separable mixture of 1-bromoacetyl-1-hydroxy*cyclo*hexanol (characterised as a crystalline pyridine adduct) (IX) and a dimer, m. p. 117—118°; the latter was resistant to boiling alcoholic potassium hydroxide and boiling dimethylaniline. Acid catalysts had a marked effect in promoting the bromination and in minimising the formation of the dimeric product.



The reaction of the ketone (VII) with one equivalent of sulphuryl chloride in light petroleum at 40° afforded the crystalline 1-chloroacetyl*cyclo*hexanol (X). Attempts to increase the yield by using an excess of sulphuryl chloride led only to the formation of complex mixtures.

The bromide (IX) when treated with silver acetate in acetic acid gave 1-acetoxyacetyl-*cyclo*hexanol (XI). The hydrolysis of the bromide (IX) to the free ketol (XII) presented considerable difficulties; the most efficacious procedure (*ca.* 50% yield) was the gradual addition of potassium hydroxide solution to the aqueous phase of a solution in *tert.*-butanol in the presence of a saturated solution of sodium chloride.

Direct oxidative acetolysis of the ketone (VII) with mercuric acetate (Treibs, *Naturwiss.*, 1948, **35**, 125) led to an intractable mixture from which none of the ketol acetate (XI) could be isolated. Again, an attempted oxidation of the ketone (VII) with selenium dioxide in dioxan gave none of the expected keto-aldehyde.

A similar series of reactions was also carried out with 1-hydroxy*cyclo*pentane-1-carboxylic acid. Bromination of 1-acetyl*cyclo*pentanol and subsequent hydrolysis afforded the 1-hydroxyacetyl compound which in our hands was an undistillable liquid. It was characterised as a semicarbazone; regeneration from the derivative again yielded a liquid which readily reduced ammoniacal silver nitrate and alkaline copper sulphate. Since our earlier communication (*loc. cit.*) Cocker, Cocker, and Lipman (*Chem. and Ind.*, 1951, 112) have described this compound as a solid, m. p. 109°.

A number of these compounds and their homologues (details of which will be published shortly) are being subjected to biological tests, the results of which will be reported elsewhere.

Experimental.

All m.p.s are uncorrected; the micro-analyses have been carried out by Dr. Sobotka, University of Graz, and in the Micro-analytical Laboratory, Organic Chemistry Department, Imperial College of Science and Technology (Mr. F. H. Oliver).

Hydrogenation of Ethyl Phenylglyoxalate.—The ester (72 g.) in acetic acid (200 c.c.) was hydrogenated at 70°/50 atmos. in the presence of the Adams's platinum catalyst (1 g.). Approximately two mols. of hydrogen were taken up (theory: 3 mols.). Raising the temperature to 125° and continuing the experiment for 5 hours did not result in further hydrogen uptake. The product was ether extracted, and the residual oil distilled through a 6" column packed with helices; the bulk distilled at 101—102°/1 mm. On redistillation the *substance* (55 g.) had b. p. 84—85°/2 × 10^{-3} mm. (bath temp. 115—120°) (Found: C, 65·8, 65·4; H, 7·7, 7·8%; *M*, 199. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%; *M*, 182). It did not decolourise bromine in chloroform but evolved hydrogen bromide on being heated. Neutral aqueous potassium permanganate was decolourised only very slowly and no keto-derivative was obtained.

Reduction of the Compound $C_{10}H_{14}O_3$.—The compound (7 g.) was dissolved in ether (100 c.c.) and, with stirring, lithium aluminium hydride (2·5 g.) was added in small portions during 0·75 hour; the mixture was then stirred at room temperature for 1 hour, acidified with hydrochloric acid (crushed ice), and extracted with ether. A *substance* (3 g.), b. p. 93—95°/7 × 10^{-3} mm., was obtained as a viscous oil which, on trituration with light petroleum (40—60°), gave a crystalline solid. Recrystallisation of this from benzene–light petroleum gave needles, m. p. 80° (Found: C, 68·2; H, 8·9. $C_9H_{12}O_3$ requires C, 68·57; H, 8·6%).

Oxidation of the Compound $C_{10}H_{14}O_3$.—The compound (4 g.), suspended in 5% aqueous sodium hydroxide, was treated dropwise at 70° with aqueous potassium permanganate (6 g.), and the reaction completed on the steam-bath for 15 minutes. The solution was filtered, cooled to 0°, and just acidified with aqueous sulphuric acid. The oil obtained by ether extraction crystallised on trituration with light petroleum. Recrystallisation from light petroleum (b. p. 100—120°) gave plates of an acid, m. p. 136—137° (Found: C, 60·5; H, 8·5%).

Ethyl 1-*Hydroxy*cyclo*hexylchloroacetate.*—This was prepared by Darzens and Lévy's method (*Compt. rend.*, 1937, **204**, 272) [the magnesium amalgam was prepared from magnesium (25 g.) and mercury (1200 g.) in a high vacuum instead of in hydrogen]. The ester (150 g.; from 100 g. of *cyclo*hexanone) had b. p. 88—90°/2 × 10^{-3} mm. (bath temp. 125—130°), n_D^{27} 1·4755 (Found: C, 54·25; H, 7·85; Cl, 16·1. Calc. for $C_{10}H_{17}O_3Cl$: C, 54·55; H, 7·7; Cl, 16·1%). Darzens and Lévy (*loc. cit.*) give b. p. 136—138/4 mm.

Reaction of the Above Chloro-ester with Potassium Hydroxide. Ethyl α : 1-*Epoxy*cyclo*hexylacetate.*—(*a*) The ester (20 g.) in dry ethanol (150 c.c.) was cooled to 0° and potassium hydroxide (5 g.) in dry ethanol (150 c.c.) was added dropwise with stirring until the solution was just alkaline (phenolphthalein). After concentration and repeated removal of the potassium chloride, distillation gave ethyl α : 1-epoxy*cyclo*hexylacetate (14·5 g.), b. p. 72°/4 × 10^{-3} mm., $n_D^{27\cdot5}$ 1·4610.

(*b*) The chloro-ester in aqueous ethanol was titrated against 2N-potassium hydroxide (phenolphthalein). On working up of the product the epoxide was again obtained; the b. p. and $n_D^{27\cdot5}$ were identical with those of the previous sample (Found: C, 65·1; H, 9·0. Calc. for $C_{10}H_{14}O_3$: C, 65·2; H, 8·8%).

Reaction of the Chloro-ester with Silver Acetate.—Ethyl 1-hydroxy*cyclo*hexylchloroacetate (15 g.) was heated under reflux with acetic acid (150 c.c.) and silver acetate (15 g.) for 4 hours. On distillation of the product, a colourless liquid (13 g.), b. p. 78°/10^{-3} mm., was obtained (Found: C, 55·3; H, 7·8; Cl, 13·2. $C_{12}H_{19}O_4Cl$ requires C, 55·0; H, 7·3; Cl, 13·5%). This is believed to be *ethyl* 1-*acetoxy*cyclo*hexylchloroacetate.*

Reactions of the Epoxide.—(*a*) The epoxide (10 g.) was heated with water at 180° for 12 hours. A considerable pressure of carbon dioxide developed; the product was extracted with ether, the extract washed with sodium hydrogen carbonate, and the solvent evaporated, and the residual oil distilled, giving *cyclo*hexanealdehyde (b. p. 157—158°) (Zelinsky and Gutt, *Ber.*, 1907, **40**, 3051, give b. p. 159—160°). The semicarbazone, m. p. 174—176° (*idem*, *ibid.*, m. p. 173—174°), separated from aqueous pyridine.

(*b*) The epoxide was recovered unchanged when a suspension in 2N-sulphuric acid was heated for 15 minutes at 100° with stiring.

(*c*) *Reduction of the epoxide.* 2-1′-*Hydroxy*cyclo*hexylethanol.* The epoxide (10 g.) was added dropwise to a solution of lithium aluminium hydride (5 g.) in absolute ether (500 c.c.) at 0°; after complete addition (1 hour) stirring was continued for 2 hours at 0° and overnight at room temperature. The mixture was decomposed with 2N-sulphuric acid (crushed ice), and the ether layer was separated and the aqueous layer extracted with chloroform (3 × 100 c.c.). The extracts were combined, washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and the solvents removed, giving 2′-1′-*hydroxy*cyclo*hexylethanol* (6·4 g.), b. p. 95°/4 × 10^{-3} mm., n_D^{25} 1·4870 (Found: C, 66·6; H, 11·2. $C_8H_{16}O_2$ requires C, 66·7; H, 11·15%).

cyclo*Hexanone Cyanohydrin.*—*cyclo*Hexanone (1000 g.) was dissolved in ether (2·5 l.), and finely powdered sodium cyanide (735 g.) added. With vigorous stirring and cooling to −15°, concentrated hydrochloric acid (1500 c.c.) was added dropwise; thereafter the temperature was kept below 0° for 6 hours. The cyanohydrin was extracted into ether, and the solution washed with saturated sodium hydrogen sulphite solution followed by aqueous sodium hydrogen carbonate and dried (Na_2CO_3), and the cyanohydrin distilled slowly (wide-bore retort), b. p. 63°/10^{-3} mm. (bath temp. 75°). When the washings were omitted or distillation was at higher pressure, decomposition occurred. The liquid

(900 g.) crystallised on cooling; recrystallisation from light petroleum gave pure *cyclo*hexanone cyanohydrin, m. p. 27—28° (Found : C, 67·1; H, 8·8; N, 11·0. Calc. for $C_7H_{11}ON$: C, 67·2; H, 8·8; N, 11·2%).

1-*Hydroxy*cyclo*hexane*-1-*carboxylic Acid*.—This was obtained by the smooth hydrolysis of the nitrile (900 g.) with concentrated hydrochloric acid (1500 c.c.) on the steam-bath for 6 hours. The acid formed needles, m. p. 110°, from benzene–light petroleum (Found : C, 58·7; H, 8·3. Calc. for $C_7H_{12}O_3$: C, 58·3; H, 8·3%), and was characterised as the 3 : 5-*dinitrobenzoate*, m. p. 165—168°, needles from ethanol (Found : C, 49·6; H, 3·9. $C_{14}H_{14}O_9N_2$ requires C, 49·7; H, 4·1%).

Reactions of the Acid with Methyl-lithium. 1-*Acetyl*cyclo*hexanol and* 2-1′-*Hydroxy*cyclo*hexylpropan*-2-*ol*.—(*a*) The acid (47 g.) in ether (1000 c.c.) was added dropwise to a solution of methyl-lithium (from 20 g. of lithium) during 3 hours, and the mixture was then stirred overnight at room temperature. The mixture was poured on crushed ice (1000 g.) and concentrated hydrochloric acid (300 c.c.), the ether layer was separated, and the aqueous layer extracted with ether (6 × 500 c.c.). After evaporation of the ether, the residual oil was fractionated; two fractions were obtained : (1) 26 g., b. p. 42—50°/10^{-4} mm.; and (2) 10 g., b. p. 60—90°/10^{-4} mm. Redistillation of (1) gave 1-acetyl*cyclo*hexanol (22 g.), b. p. 46°/10^{-4} mm. (bath temp. 60°), b. p. 57°/10^{-4} mm. (bath temp. 98°), $n_D^{24\cdot5}$ 1·4672 (Found : C, 67·4; H, 9·9. Calc. for $C_8H_{14}O_2$: C, 67·7; H, 9·9%).

Fraction (2) on trituration with light petroleum (40—60°) deposited a solid (8 g.), which when recrystallised from light petroleum (b. p. 100—120°) yielded 2-1′-*hydroxy*cyclo*hexylpropan*-2-*ol* as needles, m. p. 87° (Found : C, 67·9; H, 11·4. $C_9H_{18}O_2$ requires C, 68·3; H, 11·4%).

(*b*) In a similar experiment, in which the mixture obtained on the addition of the organic acid to the methyl-lithium solution was allowed to warm and was then heated under reflux for 1 hour, only small quantities of the ketone (4 g.) and the carbinol (10 g.) were obtained.

(*c*) Lithium metal (50 g.) in short lengths of 1-mm. ribbon was introduced into anhydrous ether (2000 c.c.) in an atmosphere of nitrogen. Methyl iodide (507 g.) in absolute ether (1000 c.c.) was added dropwise with stirring during 2 hours (carbon dioxide–acetone cooled condensers). By titration of an aliquot portion of the ethereal methyl-lithium against standard acid the metal content was found to be 40 g. 1-Hydroxy*cyclo*hexane-1-carboxylic acid (144 g.) in ether (1500 c.c.), externally cooled to 15°, was vigorously stirred and the methyl-lithium solution added dropwise (nitrogen atmosphere) until two moles had been added (3 hours). The rest of the methyl-lithium solution was run in during 0·5 hour. When the solution was worked up in the usual manner, without acidification, an oil (128 g.) was obtained, which on distillation gave 1-acetyl*cyclo*hexanol (100 g.), together with a negligible quantity of the carbinol.

Derivatives of 1-*Acetyl*cyclo*hexanol*.—The *semicarbazone* was prepared in aqueous pyridine and recrystallised from aqueous ethanol; it had m. p. 221—222° (Found : C, 54·7; H, 8·9; N, 21·2. $C_9H_{17}O_2N_3$ requires C, 54·3; H, 8·5; N, 21·1%). The *phenylhydrazone* was prepared in ether and crystallised from light petroleum (b. p. 80—100°) forming needles, m. p. 163° (decomp.) (Found : C, 72·5; H, 8·9. $C_{14}H_{20}ON_2$ requires C, 72·5; H, 8·6%). The 2 : 4-*dinitrophenylhydrazone* separated from ethanol in orange needles, m. p. 206° (decomp.) (Found : N, 16·9. $C_{14}H_{18}O_5N_4$ requires N, 17·3%).

1-*Acetyl*cyclo*hexyl benzoate*. 1-Acetyl*cyclo*hexanol (5·7 g.) was dissolved in dry pyridine (10 c.c.) and, with cooling to 0°, benzoyl chloride (5·6 g.) was added. After the reaction mixture had been heated for 2 hours at 120° and worked up in the usual manner, 1-*acetyl*cyclo*hexyl benzoate* was obtained as a viscous liquid, b. p. 124—125°/10^{-4} mm. (Found : C, 73·45; H, 7·3. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%).

Bromination of 1-*Acetyl*cyclo*hexanol*. 1-*Bromoacetyl*cyclo*hexanol*.—(*a*) The hydroxy-ketone (21·6 g.) in dry petroleum (100 c.c.; b. p. 40—43°) was treated dropwise with stirring under reflux (nitrogen atmosphere) with bromine (24 g.; during 2·5 hours). The light petroleum and residual hydrogen bromide were removed in vacuum and the viscous pale yellow liquid triturated with aqueous ethanol (60% by vol.; 100 c.c.) and cooled to −5°. After 0·5 hour the crystalline material (15 g.; m. p. 103—106°) was filtered off. The filtrate was evaporated *in vacuo* (without being heated), the residual oil taken up in a little ether, the solution dried (Na_2SO_4), the solvent removed, and the residue distilled in high vacuum; 1-*bromoacetyl*cyclo*hexanol* (14 g.) was obtained as a pale yellow liquid, b. p. 122—125°/10^{-4} mm. The bromide contained some unreacted ketone which could not be removed by fractionation. The impure bromide (2·2 g.) was therefore warmed at 60° with pyridine (1 g.) for 5 minutes and set aside at 0° for several hours. The crystalline adduct was dissolved in methanol and precipitated with ether. Recrystallisation from methanol–ether yielded the *pyridine adduct*, m. p. 148°, as needles (Found : C, 49·6; H, 6·4; N, 4·2; Br, 24·5. $C_8H_{13}O_2Br,C_5H_5N,CH_4O$ requires C, 50·5; H, 6·4; N, 4·2; Br. 24·2%).

The crystalline by-product (m. p. 103—106°) after repeated crystallisation from ethanol yielded needles, m. p. 117—118°, of a *dimer* (Found : C, 45·4; H, 5·8; Br, 36·4%; *M*, 397. $C_{16}H_{26}O_4Br_2$ requires C, 43·4; H, 5·8; Br, 36·2%; *M*, 442).

(*b*) 1-Acetyl*cyclo*hexanol (198·8 g.) was dissolved in acetic acid (198 c.c.) and bromine (74·2 c.c.) in acetic acid (1388 c.c.) was added at room temperature all in one lot. A 50% solution of hydrogen bromide in acetic acid (5 c.c.) was then added and the mixture agitated at short intervals; after 30 minutes all the bromine had reacted. The solution was diluted with ether (1000 c.c.) and poured on crushed ice (2000 g.); most of the acetic acid was neutralised with concentrated aqueous sodium hydroxide at 0°, and the solution was then carefully neutralised with aqueous sodium carbonate and thoroughly extracted into ether (8 × 500 c.c.). The ether extract was dried (Na_2SO_4) and distilled, yielding pure 1-bromoacetyl-*cyclo*hexanol (207 g.) as a viscous liquid, b. p. 70°/10^{-4} mm. (bath temp. 100°). The compound rapidly coloured in the atmosphere (Found : C, 42·4; H, 5·6; Br, 35·3. $C_8H_{13}O_2Br$ requires C, 43·3; H, 5·9; Br, 36·2%). It afforded the pyridine adduct described above.

A higher-boiling fraction, b. p. 140° (bath temp. 180°), was obtained as a viscous pale yellow oil (33 g.) which solidified when seeded with a crystal of the dimer (described above), and afforded needles (from ethanol), m. p. 117—118°. This dimer was unchanged when heated under reflux for several hours with 30% alcoholic potassium hydroxide or with dimethylaniline.

1-*Chloroacetyl*cyclo*hexanol*.—1-Acetyl*cyclo*hexanol (14·2 g.) in light petroleum (50 c.c.; b. p. 40—43°) was heated under reflux in an atmosphere of nitrogen and, with stirring, sulphuryl chloride (13·5 g.) was added dropwise during 0·5 hour. The solution was then heated under reflux for a further 0·5 hour. After distillation of the solvent, the residual oil was fractionated under reduced pressure giving the unchanged ketone (7 g.), b. p. 45—80°/10^{-5} mm. (bath temp. 90—100°), and 1-*chloroacetyl*cyclo*hexanol* (6 g.), b. p. 80—90°/10^{-5} mm. (bath temp. 100—110°); on redistillation the latter had b. p. 88°/10^{-5} mm. (bath temp. 110°), m. p. 69—70° (needles from aqueous ethanol) (Found: C, 54·5; H, 7·8; Cl, 19·8. $C_8H_{13}O_2Cl$ requires C, 54·4; H, 7·4; Cl, 20·1%).

Acetolysis of 1-*Bromoacetyl*cyclo*hexanol*. 1-*Acetoxyacetyl*cyclo*hexanol*.—The bromide (12 g.) in 50% aqueous acetic acid (500 c.c.) was heated under reflux with silver acetate (20 g.) for 1 hour, and the solution then stirred at 80° for 2 hours. After filtration and evaporation to a small bulk (60 c.c.) the filtrate was again refluxed with silver acetate (5 g.) for 1 hour. The acetic acid was neutralised and the solution ether-extracted; distillation yielded a product, b. p. 90°/3 × 10^{-4} mm., which solidified on cooling; crystallisation from light petroleum afforded 1-*acetoxyacetyl*cyclo*hexanol* (4 g.) as rods, m. p. 42—43° (Found: C, 60·25; H, 8·24. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·0%).

The same compound could be obtained in lesser yields by the acetolysis of the bromide in glacial acetic acid, fused sodium or potassium acetate being used instead of silver acetate.

The ketol acetate (0·5 g.), aqueous pyridine (5 c.c.), and semicarbazide hydrochloride (1 g.) at 0° overnight slowly deposited the *semicarbazone* (0·3 g.), which recrystallised from hot water in long needles, m. p. 171—172° (Found: C, 51·05; H, 7·65; N, 16·5. $C_{11}H_{19}O_4N_3$ requires C, 51·35; H, 7·4; N, 16·35%).

1-*Hydroxyacetyl*cyclo*hexanol*.—(*a*) The bromide (100 g.) in 60% aqueous ethanol, was rapidly treated under nitrogen with sodium hydroxide (18·5 g.) dissolved in 60% aqueous ethanol (500 c.c.).[5] After 5 minutes the excess of alkali was neutralised with aqueous acetic acid (phenolphthalein), and the solution then concentrated in a vacuum (bath temp. 40°) to 100 c.c. By ether extraction of this concentrate an oil which solidified was obtained; when crystallised from ether–light petroleum this gave needles (29 g.), m. p. 86—87°. Although the alcohol could not be distilled without decomposition it readily sublimed in a high vacuum, giving needles, m. p. 89—90° (Wagner and Moore, *loc. cit.*, give 86—87°) (Found: C, 61·0; H, 8·9. Calc. for $C_8H_{14}O_3$: C, 60·8; H, 8·9%).

(*b*) The bromide (100 g.) was dissolved in *tert.*-butanol (200 c.c.), and a saturated aqueous solution of sodium chloride (250 c.c.) added. With vigorous shaking, potassium hydroxide (20·8 g.) in water (250 c.c.) was added in ten portions during 15 minutes, allowing neutralisation of each portion (phenolphthalein). After complete addition the mixture was just acidified with aqueous sulphuric acid and the aqueous layer saturated with sodium chloride. The *tert.*-butanol layer was separated and the aqueous layer thoroughly extracted with chloroform (5 × 100 c.c.). The extracts were dried (Na_2SO_4) and the solvents distilled off; an almost colourless liquid remained which solidified on cooling. 1-Hydroxyacetyl*cyclo*hexanol (38 g.), m. p. 88—89°, was obtained after a single crystallisation from ether–light petroleum (b. p. 40—60°).

1-*Acetyl*cyclo*pentanol*.—*cyclo*Pentanone cyanohydrin was obtained as described for the hexanone cyanohydrin, but unlike the latter it could not be distilled without decomposition even in a high vacuum. The crude cyanohydrin (500 g.) was readily hydrolysed by hydrochloric acid (1000 c.c.) to yield needles (from benzene–light petroleum) of 1-hydroxy*cyclo*pentane-1-carboxylic acid (325 g.), m. p. 103—105° (Wislicenus and Gastner, *Annalen*, 1893, **257**, 333, give m. p. 103°).

The acid (153 g.) was treated with an ethereal solution of methyl-lithium (lithium content, 51 g.). After the mixture had been stirred overnight and the lithium complex decomposed with water, the solution was constantly extracted with ether (24 hours). 1-*Acetyl*cyclo*pentanol* (81·6 g.) had b. p. 72°/10 mm. (bath temp. 135—140°), n_D^{19} 1·4650 (Found: C, 65·8; H, 9·3. $C_7H_{12}O_2$ requires C, 65·6; H, 9·3%).

The *semicarbazone* separated slowly from aqueous pyridine, forming needles (from ethanol), m. p. 206—208° (decomp.) (Found: C, 52·4; H, 8·1; N, 23·1. $C_8H_{15}O_2N_3$ requires C, 51·9; H, 8·1; N, 22·7%).

1-*Acetyl*cyclo*pentyl Acetate*.—The ketone (11·5 g.) was dissolved in pyridine (15 c.c.), acetic anhydride (15 c.c.) added at 0°, and the mixture refluxed for 2 hours. The *acetate* (10 g.) had b. p. 100—103°/10 mm. (Found: C, 63·7; H, 8·6. $C_9H_{14}O_3$ requires C, 63·5; H, 8·2%).

Bromination of the Ketone. 1-*Bromoacetyl*cyclo*pentanol*.—1-Acetyl*cyclo*pentanol (5·8 g.) was dissolved in acetic acid (10 c.c.), and bromine (2·5 c.c.) in acetic acid (100 c.c.) added in one lot, followed by a 50% solution of hydrogen bromide in acetic acid (0·5 c.c.). After 15 minutes decolorisation of the bromine occurred, and the solution was worked up in the usual manner. Distillation yielded 1-*bromoacetyl*cyclo*pentanol* (7·2 g.), b. p. 85—95°/10^{-4} mm. (slight decomposition during distillation) (Found: Br, 38·1. $C_7H_{11}O_2Br$ requires Br, 38·6%).

Hydrolysis of the Bromide.—The bromide (7·2 g.) in 60% aqueous ethanol (60 c.c.) was treated in the usual manner with sodium hydroxide (1·35 g.) in 60% aqueous ethanol (30 c.c.). The product was isolated as an oil which could not be distilled. It was dissolved in aqueous pyridine (5 c.c.) and treated with semicarbazide hydrochloride (5 g.) in water (5 c.c.); after 24 hours at 0° the crystalline precipitate (2 g.) was collected, and recrystallisation afforded 1-*hydroxyacetyl*cyclo*pentanol semicarbazone* as microneedles, m. p. 211° (decomp.) (Found: C, 47·8; H, 7·2; N, 20·9. $C_8H_{15}O_2N_3$ requires C, 47·8; H, 7·4; N, 20·9%).

The semicarbazone was suspended in light petroleum and stirred at 70° for 0·5 hour with 2N-sulphuric acid (15 c.c.). On evaporation of the petroleum layer a liquid was obtained which reduced ammoniacal silver nitrate solution and alkaline copper sulphate solution. The liquid could not, however, be distilled without decomposition even in a high vacuum.

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DEPARTMENT OF CHEMICAL PATHOLOGY,
WESTMINSTER MEDICAL SCHOOL, LONDON, S.W.1. [*Received, July 14th*, 1951.]

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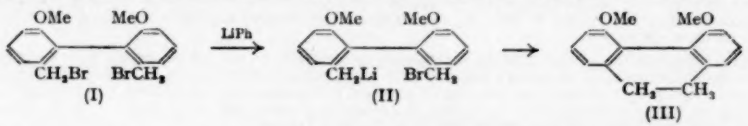
679. 9 : 10-*Dihydrophenanthrenes. Part II.** 9 : 10-*Dihydro-*4 : 5-*dimethoxyphenanthrene.*

By D. MURIEL HALL and E. E. TURNER.

9 : 10-Dihydro-4 : 5-dimethoxyphenanthrene is formed in low yield by the interaction of phenyl-lithium and 2 : 2′-bisbromomethyl-6 : 6′-dimethoxydiphenyl.

9 : 10-DIHYDROPHENANTHRENE can readily be obtained by the action of phenyl-lithium on 2 : 2′-bisbromomethyldiphenyl (Hall, Lesslie, and Turner, *J.*, 1950, 711). It was considered that the method might be generally applicable to the preparation of substituted 9 : 10-dihydrophenanthrenes and, in particular, to the preparation of 4 : 5-disubstituted dihydrophenanthrenes which would be of considerable stereochemical interest. In fact we find that the action of phenyl-lithium on 2 : 2′-bisbromomethyl-6 : 6′-dimethoxydiphenyl (I) gives only a poor yield of 9 : 10-dihydro-4 : 5-dimethoxyphenanthrene (III), isolated after tedious fractional crystallisation. The main product was a complex mixture, evidently more complex than dimeric material such as would have arisen from interaction at only one of the 2 : 2′-groups. It is probable that the presence of additional groups in the 6 : 6′-positions in the diphenyl prevents the sufficiently close approach of the methyl-lithium and the bromomethyl groups in the intermediate compound (II). The final product (III) must also be somewhat

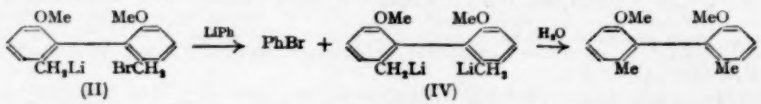


(I) (II) (III)

strained since the normal twist of the dihydrophenanthrene system is insufficient to accommodate the two methoxyl groups without bringing into play their mutual repulsive forces.

By heating 9 : 10-dihydro-4 : 5-dimethoxyphenanthrene with sulphur we obtained a small amount of 4 : 5-dimethoxyphenanthrene, isolated as the picrate. The corresponding dihydrophenanthrene does not form a picrate and most of it was recovered unchanged from the attempted dehydrogenation (cf. Krueger and Mosettig, *J. Org. Chem.*, 1938, **3**, 340, who were unable to dehydrogenate 9 : 10-dihydro-4-methoxyphenanthrene without removal of the methoxyl group).

The possibility of an alternative course of reaction between the dibromide and phenyl-lithium, in which the dilithium compound (IV) might be formed, was considered.

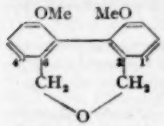


(II) (IV)

This would be decomposed by water to give 6 : 6′-dimethoxy-2 : 2′-ditolyl (Me = 2), which might also be expected to undergo dehydrogenation with the formation of 4 : 5-dimethoxyphenanthrene when heated with sulphur.

* Part I, *J.*, 1950, 711.

For three reasons we consider the former course of reaction to be that followed : (1) The analytical values are much closer to those required for the dihydrophenanthrene than to those for the ditolyl. (2) The ultra-violet absorption spectrum corresponds more closely to a hindered dihydrophenanthrene than to a hindered ditolyl (unpublished work). (3) For given amounts of lithium and of dibromide the former reaction leads to more ionic bromide than the latter (since in the latter some remains as bromobenzene) and this larger amount was observed experimentally.



6 : 6′-Dimethoxydiphenic acid was prepared as described in the literature, with minor but significant modifications. Its dimethyl ester was reduced with excess of lithium aluminium hydride. The resulting diol could readily be converted into the cyclic ether, 2 : 7-dihydro-4′ : 1″-dimethoxy-3 : 4-5 : 6-dibenzoxepine (inset), by warming it with 50% sulphuric acid. Treatment of the diol with an excess of phosphorus tribromide gave 2 : 2′-bisbromomethyl-6 : 6′-dimethoxydiphenyl.

The ultra-violet absorption spectra of 9 : 10-dihydro-4 : 5-dimethoxyphenanthrene and of 2 : 7-dihydro-4′ : 1″-dimethoxy-3 : 4-5 : 6-dibenzoxepine are discussed in a later paper.

Experimental.

3-*Methoxy*-2-*nitrotoluene*.—2-Nitro-*m*-cresol was prepared by Gibson's method (*J.*, 1923, **123**, 1269) with the modification proposed by Kenner and Turner (*J.*, 1928, 2340). The crude product from steam-distillation was dissolved in xylene and dried over sodium sulphate before methylation by Haworth and Lapworth's method (*J.*, 1923, **123**, 2982). In later runs the volume of xylene used was increased by 33% and the methyl sulphate added in 3—4 lots with vigorous shaking. Under these conditions methylation appeared to be complete in less than an hour instead of the 18 hours recorded by Haworth and Lapworth. The overall yield based on *m*-cresol was 60%.

3-*Methoxy*-2-*nitrobenzoic Acid*.—Initially the 3-methoxy-2-nitrotoluene was oxidised in 5-g. batches with potassium permanganate (16 g. in 600 c.c. of water) in presence of hydrated magnesium sulphate (12 g.). Boiling under reflux was continued for 12 hours. Later, 15-g. batches were oxidised with 80 g. of permanganate in 2 l. of water in presence of 36 g. of hydrated magnesium sulphate, with 19 hours' boiling. In both series the permanganate solution was added at intervals during the oxidation. The acid was isolated by passing in sulphur dioxide, separated from a small quantity of non-acidic material by dissolution in aqueous sodium hydrogen carbonate, reprecipitated, and crystallised from aqueous alcohol. The yield was 60—65%, and the m. p. 255—256°.

6 : 6′-*Dimethoxydiphenic Acid*.—The nitro-acid was reduced by Pschorr's method (*Annalen*, 1912, **391**, 23), and the resulting 2-amino-3-methoxybenzoic acid (33·5 g., 1 mol.) diazotised as described by Wittig and Petri (*Annalen*, 1933, **505**, 17). The following catalyst gave a better yield more quickly. Copper sulphate (48·5 g.) was dissolved in water (275 c.c.) and ammonia (*d* 0·88; 55 c.c.), and sodium metabisulphite (110 g.) and ammonia (110 c.c.) were added just before final use. The catalyst solution was cooled to about 30° and the diazo-solution added with rapid stirring, followed by a solution of anhydrous ferric chloride (72 g.) in water (110 c.c.) and concentrated hydrochloric acid (360 c.c.). The precipitated 6 : 6′-dimethoxydiphenic acid (26 g., 87%), after dissolution in sodium hydrogen carbonate solution and reprecipitation, had m. p. 296—298°.

The dimethyl ester was obtained by heating the acid (30 g.) with methyl alcohol (400 c.c.) and concentrated sulphuric acid (30 g.) for 6 hours under reflux. The yield, after one crystallisation from methyl alcohol, was 30·5 g. (92%), and the m. p. 136·5—137·5.

2 : 2′-*Bishydroxymethyl*-6 : 6′-*dimethoxydiphenyl*.—The ester was very sparingly soluble in ether and was accordingly added to the lithium aluminium hydride (3·5 g., 2·5 mols.) in ether (250 c.c.) as a finely ground solid (12 g.), each lot being washed into the reaction flask with ether (300 c.c. altogether). The reaction was completed by ½ hour's boiling under reflux. Diluted sulphuric acid was added, the ether distilled off from the reaction vessel, and the solid filtered off. 2 : 2′-*Bishydroxymethyl*-6 : 6′-*dimethoxydiphenyl* crystallised from alcohol in rods (9 g., 90%), m. p. 158—159° (Found : C, 70·1; H, 6·7. $C_{16}H_{18}O_4$ requires C, 70·1; H, 6·6%). Warming this for a few minutes with an excess of 50% sulphuric acid gave 2 : 7-*dihydro*-4′ : 1″-*dimethoxy*-3 : 4-5 : 6-*dibenzoxepine*, which crystallised from alcohol in needles, m. p. 136° (Found : C, 74·9; H, 6·7. $C_{16}H_{16}O_2$ requires C, 75·0; H, 6·3%).

2 : 2′-*Bisbromomethyl*-6 : 6′-*dimethoxydiphenyl* (I).—The finely ground diol (9 g., 1 mol.) was added gradually to phosphorus tribromide (54 g., 6 mols.) with ice-cooling. The vigorous reaction was completed by keeping the mixture at room temperature for ½ hour and finally warming it to *ca.* 30° for 15 minutes. The product was poured on crushed ice, and the sticky *dibromide* which separated was ground with water. It was dried in a vacuum-desiccator over sodium hydroxide and crystallised once from light petroleum (b. p. 80—100°) (yield 9·5 g., 71%; m. p. 111—113°). Rapid recrystallisation from methyl alcohol gave a product, m. p. 113—115°, but was accompanied by some loss. Repeated crystallisation from light petroleum or methyl alcohol raised the m. p. to 115° (Found : C, 48·7; H, 4·3; Br, 39·6. $C_{16}H_{16}O_2Br_2$ requires C, 48·0; H, 4·0; Br, 39·9%).

9 : 10-*Dihydro*-4 : 5-*dimethoxyphenanthrene* (III).—(1) Finely ground 2 : 2′-bisbromomethyl-6 : 6′-dimethoxydiphenyl (9 g.), in warm ether (300 c.c.), was added gradually to an ethereal solution of phenyl-lithium (from 0·42 g. of lithium and 4·5 g. of bromobenzene). Solid immediately separated. Water was added and the solid, which was insoluble in both water and ether, was filtered off (*ca.* 3·5 g.). It had an indefinite m. p. and after repeated attempts at crystallisation and purification it was discarded. The ethereal solution was dried and distilled under reduced pressure. The main fraction

(2·4 g.) had b. p. 210—240°/12 mm. and eventually solidified. Repeated crystallisations from methyl alcohol and from light petroleum (b. p. 60—80°), accompanied where possible by mechanical separation of two types of crystals, finally gave very small amounts of (*a*) the original dibromide (mixed m. p. not depressed) and (*b*) needles, m. p. 133—134°, which proved to be 9 : 10-*dihydro*-4 : 5-*dimethoxyphenanthrene* (Found: C, 80·2; H, 6·7. $C_{16}H_{14}O_2$ requires C, 80·0; H, 6·7. Calc. for 6 : 6′-dimethoxy-2 : 2′-ditolyl, $C_{14}H_{18}O_2$: C, 79·3; H, 7·5%).

(2) The experiment was repeated using a larger volume of ether (500 c.c. altogether), a larger excess of phenyl-lithium (from 0·70 g. of lithium and 7·9 g. of bromobenzene), with vigorous stirring during the slow addition of the dibromide. A negligible amount of the insoluble solid was obtained on addition of water. Ether was distilled off from the ethereal layer and the residue extracted repeatedly with light petroleum (b. p. 80—100°). The extracts deposited gums and some crystals; these were repeatedly extracted with various fractions of light petroleum and any crystalline products obtained repeatedly crystallised from light petroleum and from methyl alcohol. Finally, 0·6 g. (11%) of 9 : 10-dihydro-4 : 5-dimethoxyphenanthrene, m. p. 130—133°, was obtained (mixed m. p. with previous specimen not depressed). No unchanged dibromide was detected in the product. The total bromide in the combined aqueous solutions was precipitated as silver bromide (15·5 g.). For an initial weight of lithium of 0·70 g. the dihydrophenanthrene reaction requires 13·7 g. of silver bromide, and the ditolyl reaction 9·5 g. The amount found is consistent with the dihydrophenanthrene reaction and an initial lithium weight of 0·83 g., an amount within the experimental error in view of the difficulty of weighing the lithium as wire: for the ditolyl reaction the amount of silver bromide found would require an initial lithium weight of 1·22 g.

Dehydrogenation of 9 : 10-*Dihydro*-4 : 5-*dimethoxyphenanthrene*.—9 : 10-Dihydro-4 : 5-dimethoxyphenanthrene (0·1055 g., 1 mol.) and sulphur (0·0141 g., 1 atom) were heated in a metal-bath at about 220° for 4 hours. The residue was extracted with alcohol and boiled with charcoal, and the filtered solution concentrated to about 60 c.c. An excess of alcoholic picric acid was added and long scarlet needles of 4 : 5-*dimethoxyphenanthrene picrate* slowly separated (0·06 g.), m. p. 191—193° (Found: C, 56·2; H, 3·7; N, 9·2. $C_{22}H_{17}O_9N_3$ requires C, 56·5; H, 3·7; N, 9·0%). By washing of the filtrate with sodium hydroxide and extraction with ether, unchanged 9 : 10-dihydro-4 : 5-dimethoxyphenanthrene was recovered.

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BEDFORD COLLEGE, UNIVERSITY OF LONDON. [*Received, July 21st*, 1951.]

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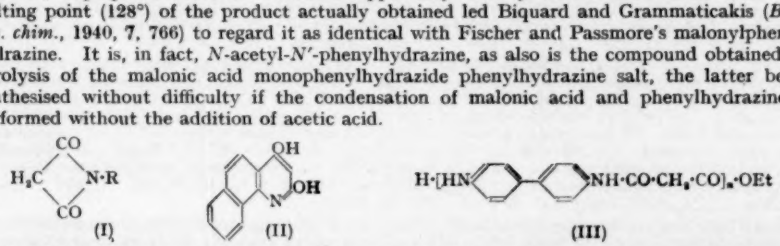
680. *The Structures of Some Supposed Azetid-2 : 4-diones. Part I. Derivatives of Malonic Acid.*

By F. E. KING, J. W. CLARK-LEWIS, and C. R. P. MORGAN.

Evidence is given in support of the conclusions already published (*J.*, 1949, 1318) that the supposed *N*-(phenylamino)- and *N*-1-naphthyl-malonimide are respectively *N*-acetyl-*N*′-phenylhydrazine and 2 : 4-dihydroxy-7 : 8-benzoquinoline, and that malonylbenzidine is not a cyclic imide but a substance of polymeric nature.

A REINVESTIGATION of several compounds hitherto formulated as malonimides has shown that they do not possess the constitutions formerly attributed to them (see King, *J.*, 1949, 1318). One of these is the so-called malonylphenylhydrazine (I; R = Ph·NH·), m. p. 128°, of E. Fischer and Passmore (*Ber.*, 1889, **22**, 2735), said to be a pyrolysis product of the phenylhydrazine salt of malonic acid monophenylhydrazide. This phenylhydrazine salt cannot, however, be prepared under the conditions apparently used by Fischer and Passmore, and the melting point (128°) of the product actually obtained led Biquard and Grammaticakis (*Bull. Soc. chim.*, 1940, **7**, 766) to regard it as identical with Fischer and Passmore's malonylphenylhydrazine. It is, in fact, *N*-acetyl-*N*′-phenylhydrazine, as also is the compound obtained on pyrolysis of the malonic acid monophenylhydrazide phenylhydrazine salt, the latter being synthesised without difficulty if the condensation of malonic acid and phenylhydrazine is performed without the addition of acetic acid.



"N-1-*Naphthylmalonimide*."—By the action of boiling ethyl malonate on α-naphthylamine, Baumgarten and Kärgel (*Ber.*, 1927, **60**, 841) prepared 2 : 4-dihydroxy-7 : 8-benzoquinoline (II); they were apparently unaware that under very similar conditions R. Meyer (*Annalen*,

1906, **347**, 23) had previously obtained a compound which he had described as α-naphthylmalonimide (I; R = α-$C_{10}H_7$). Repetition of both preparations has given products that are indistinguishable, both forming with nitrous acid the red hydroxyimino-derivative already described (Baumgarten and Kärgel, *loc. cit.*). Support for the dihydroxyquinoline structure (II) was found in the formation with diazomethane of an alkali-soluble monomethyl ether, and in the preparation, using phosphorus pentachloride, of 2 : 4-dichloro-7 : 8-benzoquinoline (Albert, Brown, and Duewell, *J.*, 1948, 1292). The latter product resisted catalytic hydrogenation but was partly reduced with hydriodic acid and phosphorus to 2(or 4)-iodo-7 : 8-benzoquinoline. Heating the dichlorobenzoquinoline with zinc dust gave 7 : 8-benzoquinoline, analysed as a picrate and identified by comparison of its sulphate and 2 : 4 : 6-trinitrobenzene derivative with those of a specimen obtained by the Skraup synthesis. Zinc dust distillation of 2 : 4-dihydroxy-7 : 8-benzoquinoline, believed by Baumgarten and Kärgel from the melting point of the product (51°) and of its sulphate (213°) to result in the formation of 7 : 8-benzoquinoline, has been found to give α-naphthylamine (m. p. 51°; sulphate, m. p. 220°).

Malonylbenzidine.—The foregoing identification indicated a possible alternative structure for "malonylbenzidine," a product formed under comparable conditions from ethyl malonate and benzidine and first prepared by Remfry (*J.*, 1911, **99**, 610). The compound was re-examined by Le Fèvre (*J.*, 1929, 733), and on the results of nitrogen analyses of an amorphous sulphate and of a crystalline derivative formed from salicylaldehyde in boiling phenol, Remfry's macro-ring formula of the Kaufler type was replaced by the structure (I; R = *p*-*p*′-$H_2N{\cdot}C_6H_4{\cdot}C_6H_4$). The supposed malonimide is said also to have been obtained by heating ethyl *N*-(4′-amino-4-diphenylyl)malonamate (Mehta and Thosar, *J. Indian Chem. Soc.*, 1938, **15**, 629). However, the product prepared by Remfry's method was shown not to be a dihydroxyquinoline from its insolubility in aqueous alkalis; moreover, heating it with 70% sulphuric acid resulted in a nearly quantitative recovery of benzidine. On the other hand, the properties of malonylbenzidine, which is amorphous and chars without melting when heated, are not those expected from the constitution (I; R = *p*-*p*′-$H_2N{\cdot}C_6H_4{\cdot}C_6H_4$). It is virtually non-basic, and analysis of the supposed sulphate, precipitated on pouring a concentrated sulphuric acid solution into water, revealed that the sulphur content varied from batch to batch and was only some 10% of that required by the formula $(C_{15}H_{12}O_2N_2)_2,H_2SO_4$. Re-examination of the salicylaldehyde reaction showed that the compound of m. p. *ca.* 300° formed after short heating is heterogeneous and contains disalicylidenebenzidine, m. p. 260°, which is the sole product after 1½ hours' heating. In contrast, monoacetylbenzidine forms a crystalline acid sulphate and a salicylidene compound, and it can therefore be concluded that malonylbenzidine is a polycondensation product of type (III).

Experimental.

Malonic Acid Monophenylhydrazide Phenylhydrazine Salt.—Fischer and Passmore (*loc. cit.*) do not specify the acetic acid concentration, but from their other experiments on phenylhydrazides it is assumed to be 50%. By use of the recommended proportions, and heating on a steam-bath for 2 hours, a good yield of acetylphenylhydrazine was obtained, m. p. and mixed m. p. after recrystallisation from water, 128° (Found: C, 63·8; H, 6·6; N, 18·8. Calc. for $C_8H_{10}ON_2$: C, 64·1; H, 6·6; N, 18·7%). The identity of the product was confirmed by the formation of diacetylphenylhydrazine, m. p. 108°, on further acetylation. The required hydrazine salt was formed by heating under reflux for 2 hours a solution of malonic acid (20 g.) and phenylhydrazine (60 g.) in water (320 c.c.). Cooling precipitated a brownish solid which when crystallised from water gave the colourless compound (58 g.) described by Fischer and Passmore, having m. p. 142°—not, as recently stated (*J.*, 1949, 1326), 154°, which is the m. p. of the free malonic acid monophenylhydrazide (Found: C, 59·8; H, 5·6; N, 19·2. Calc. for $C_{15}H_{14}O_3N_4$: C, 59·6; H, 6·0; N, 18·5%).

The dried salt, in a flask fitted with a Bunsen valve, was heated in a bath at 200° and kept at this temperature for 15 minutes. The dark gummy residue was dissolved in hot ethyl acetate, and the colourless solid which separated from the cooled solution was identified by m. p. and mixed m. p. 128°, as acetylphenylhydrazine. On concentration of the residual ethyl acetate solution a further product separated which after recrystallisation from aqueous ethanol had m. p. 188°, alone or mixed with malonic bisphenylhydrazide (Found: C, 63·7; H, 5·1. Calc. for $C_{15}H_{16}O_2N_4$: C, 63·4; H, 5·6%).

2 : 4-*Dihydroxy*-7 : 8-*benzoquinoline.*—By repetition of Meyer's experiment, 2 : 4-dihydroxy-7 : 8-benzoquinoline (II) was obtained after crystallisation from ethanol–ethoxyethanol, as colourless needles, m. p. 326° (yield 25%). As lately reported by Albert, Brown, and Duewell (*loc. cit.*), Baumgarten and Kärgel's method is much less successful than has been claimed, but by heating equimolecular quantities of ethyl malonate and α-naphthylamine vigorously under reflux over a free flame until the mixture is almost solid (30—45 minutes) and working up in the usual way, yields of approx. 50% are readily obtained.

2(4)-*Hydroxy*-4(2)-*methoxy*-7 : 8-*benzoquinoline.*—The dihydroxyquinoline (II) (2 g.) was treated with excess of ethereal diazomethane, and the mixture occasionally shaken during 4 hours. Crystallisation of the insoluble bright yellow powder (2 g.), m. p. *ca.* 274°, from ethanol gave the *monomethyl*

ether as yellow needles, m. p. 286° (Found : C, 74·1; H, 4·8; N, 6·3; OMe, 14·2. $C_{14}H_{11}O_3N$ requires C, 74·6; H, 4·9; N, 6·2; OMe, 13·8%). The derivative dissolved in hot aqueous sodium hydroxide, giving a sodium salt which separated from the cold solution as colourless plates. The ether was soluble also in hot concentrated hydrochloric acid, crystallising unchanged as the solution cooled.

2 : 4-*Dichloro*-7 : 8-*benzoquinoline*.—Before its preparation with phosphoryl chloride was described by Albert, Brown, and Duewell (*loc. cit.*), 2 : 4-dichloro-7 : 8-benzoquinoline was obtained by heating in an oil-bath at 135—140° for 2½ hours a mixture of the dihydroxybenzoquinoline (5 g.) and phosphorus pentachloride (30 g.) moistened with phosphoryl chloride. After removal of the phosphoryl chloride under reduced pressure the crude product was isolated by pouring the residue into a mixture of ice and aqueous ammonia. Repeated crystallisation of the dried yellow-brown solid (5 g.) from alcohol (charcoal) gave the dichlorobenzoquinoline in colourless needles, m. p. 132° (Found : C, 62·4; H, 2·4; N, 5·6; Cl, 28·1. Calc. for $C_{13}H_7NCl_2$: C, 62·9; H, 2·8; N, 5·7; Cl, 28·6%). Small specimens could be obtained pure by distillation in steam in which the compound is very slightly volatile.

2(or 4)-*Iodo*-7 : 8-*benzoquinoline*.—A mixture of 2 : 4-dichloro-7 : 8-benzoquinoline (2 g.) and red phosphorus (2 g.) was heated with hydriodic acid (45 c.c.; *d* 1·7) under reflux for 8 hours. The hot solution was then filtered and the light yellow solid which separated on cooling was collected and triturated with aqueous sodium hydroxide and ether. Evaporation of the ethereal solution gave pale yellow crystals (0·5 g.), m. p. *ca.* 120°, which on crystallisation from light petroleum formed very pale yellow rods, m. p. 120° (Found : C, 51·3; H, 2·6; N, 4·4; I, 40·2. $C_{13}H_8NI$ requires C, 51·2; H, 2·6; N, 4·6; I, 41·6%).

7 : 8-*Benzoquinoline*.—(i) The crude mixture of bases obtained from α-naphthylamine (50 g.) by the Skraup reaction (Bamberger and Stettenheimer, *Ber.*, 1891, **24**, 2472; Haid, *Monatsh.*, 1906, **27**, 318) was distilled at atmospheric pressure. The fraction, b. p. 320—340°, consisting of 7 : 8-benzoquinoline (18·5 g., 31%), readily solidified to a mass of prisms, m. p. 51° (cf. Haid, *loc. cit.*). It was shown by the diazotisation test to be free from α-naphthylamine, and when crystallised from alcohol gave colourless prisms, m. p. 51·5—52°. The hydrogen sulphate separated from alcohol as pale yellow needles, m. p. 210° (Found : C, 56·8; H, 4·0; N, 5·2. Calc. for $C_{13}H_9N,H_2SO_4$: C, 56·3; H, 4·0; N, 5·1%), and the 1 : 3 : 5-trinitrobenzene compound from aqueous ethanol as light yellow needles, m. p. 133°.

(ii) A mixture of 2 : 4-dichloro-7 : 8-benzoquinoline (5 g.) and zinc dust (20 g.) was heated in batches (5 g.) in a current of hydrogen. The distillate (0·75 g.) was purified through its hydrogen sulphate which was recrystallised from ethanol and was identified as 7 : 8-benzoquinoline by the m. p.s and mixed m. p.s of the sulphate and of the 1 : 3 : 5-trinitrobenzene compound. The base was further characterised by a picrate, yellow needles (from alcohol), m. p. 178° (Found : N, 13·2. Calc. for $C_{13}H_9N,C_6H_3O_7N_3$: N, 13·7%).

Zinc Dust Distillation of 2 : 4-*Dihydroxy*-7 : 8-*benzoquinoline*.—A mixture of the dihydroxybenzoquinoline (5 g.) and zinc dust (25 g.), heated in portions (6 g.) in a current of hydrogen, gave a low-melting base (0·65 g.) which responded to the diazotisation test for a primary amine. The acid-soluble portion of the product, m. p. 51°, formed a sulphate, m. p. 220° alone or mixed with α-naphthylamine sulphate, and a 1 : 3 : 5-trinitrobenzene compound, m. p. 212° undepressed by the corresponding α-naphthylamine derivative (Found : C, 54·2; H, 3·2. Calc. for $C_{19}H_9N,C_6H_3O_6N_3$: C, 53·9; H, 3·4%).

"*Malonylbenzidine*."—Prepared by Remfry's method (*loc. cit.*), "malonylbenzidine" is a light brown amorphous powder insoluble in all organic solvents including phenol, camphor, and diphenylamine, thus precluding molecular-weight determinations. A specimen (2 g.) heated with sulphuric acid (20 c.c., 70%) at 150° for 2 hours gave a crystalline mass which, when triturated with water and dried, afforded benzidine sulphate (2·1 g., 95%).

Malonylbenzidine (2 g.) was ground in cold concentrated sulphuric acid (25 c.c.) and, after passing through a sintered-glass filter, the solution was poured into water. The gelatinous buff-coloured precipitate was washed by centrifuging it with water and then acetone and was dried at 100° [Found : C, 69·1, 68·8; H, 5·4, 5·5; N, 10·3, 10·6; S, 0·5. Calc. for $(C_{15}H_{12}O_2N_2)_2,H_2SO_4$: C, 59·8; H, 4·4; N, 9·3; S, 5·3%].

When a mixture of malonylbenzidine (2 g.), salicylaldehyde (6 c.c.), and phenol (20 g.) was heated under reflux for 30 minutes, a yellow solid was obtained which crystallised from phenol in plates, m. p. 298—300°. Treatment with boiling benzene in a Soxhlet apparatus left an insoluble amorphous material, m. p. 347° (decomp.), and gave disalicylidenebenzidine, m. p. 260° alone or mixed with an authentic specimen (Found : C, 79·5; H, 4·9; N, 7·1. Calc. for $C_{26}H_{20}O_2N_2$: C, 79·6; H, 5·1; N, 7·1%).

When the preparation was repeated with 1½ hours' heating under reflux the product (90%) consisted of the salicylidene derivative, m. p. and mixed m. p. 260°.

N-*Acetylbenzidine*.—The monoacetylbenzidine, m. p. 199°, was prepared by Cain's method (*J.*, 1909, **95**, 717). Its alcoholic solution, treated with 2N-sulphuric acid, gave a gelatinous precipitate (cf. Schmidt and Schultz, *Ber.*, 1879, **12**, 489; *Annalen*, 1881, **207**, 332) which when dissolved in boiling water (400 c.c./g.) gave N-*acetylbenzidine sulphate* in shining plates, m. p. 312° (decomp.) with previous discoloration (Found : C, 58·8; H, 5·8; N, 9·6; S, 5·9. $C_{28}H_{28}O_2N_4,H_2SO_4,H_2O$ requires C, 59·1; H, 5·7; N, 9·8; S, 5·6. Found, after drying at 140° : C, 61·2; H, 5·1; N, 9·9; loss, 3·7. $C_{28}H_{28}O_2N_4,H_2SO_4$ requires C, 61·1; H, 5·5; N, 10·2; loss 3·2%). N-*Acetyl*-N'-*salicylidenebenzidine* crystallised from ethanol in yellow plates, m. p. 280—281° (Found : C, 76·0; H, 5·5; N, 8·3. $C_{21}H_{18}O_2N_2$ requires C, 76·3; H, 5·5; N, 8·5%).

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.
THE UNIVERSITY, NOTTINGHAM.

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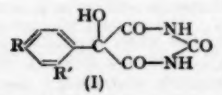
681. *The Structures of Some Supposed Azetid-2 : 4-diones. Part II.* Derivatives of Tartronic Acid.*

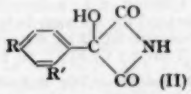
By F. E. King and J. W. Clark-Lewis.

It has been shown by direct comparison with authentic specimens that compounds prepared by the method of Riebsomer *et al.* (*J. Amer. Chem. Soc.*, 1939, **61**, 3491) from aryltartronic esters and urea or ammonia are not tartronimides but 5-aryloxazolid-2 : 4-diones. Other supposed tartronimides obtained by the alkaline degradation of 5-aryldialuric acids have already been recognised as oxazolid-diones (see *J.*, 1949, addendum to p. 1327).

Alloxan reacts with aromatic amines by condensation with the activated benzene nucleus to form 5-aryldialuric acids (I), a synthesis first recorded by Pellizzari (*Gazzetta*, 1887, **17**, 409; 1888, **18**, 340; 1889, **19**, 397; 1911, **41**, 21). These acids are decomposed when dissolved in aqueous alkalis giving ammonia, carbon dioxide, and new products which Pellizzari formulated as tartronimides (II). Pellizzari's synthesis of dialuric acids from alloxan and aromatic amines was later extended by Boehringer to phenols and aryl ethers and was protected by patents as providing, by alkaline and acid hydrolysis respectively, a route to the aryltartronic acids and the corresponding aromatic aldehydes (cf. " Friedländer," Vol. V, pp. 117, 863; Vol. VI, pp. 158 *et seq.*).

An account is now given of the alkaline degradation of 5-(2 : 4-dimethoxyphenyl)dialuric acid (I; R = R′ = OMe), first prepared by N. M. Green (Thesis, Oxford, 1948). Heating this acid with 10N-aqueous sodium hydroxide gave 2 : 4-dimethoxyphenyltartronic acid,


(I)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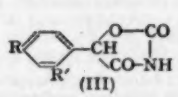
(III)

from which the related mandelic acid was obtained by treatment with warm dilute hydrochloric acid. On the other hand, the product formed on hydrolysis with N-sodium hydroxide contains one active hydrogen per molecule and gives an alkali-insoluble monomethyl ether which does not yield an acetyl derivative, facts excluding the tartronimide structure (II; R = R′ = OMe) but readily explicable on the supposition that it is an oxazolid-2 : 4-dione (III; R = R′ = OMe). This interpretation is in agreement with the comparable observations by Aspelund on other dialuric acids (*Acta Acad. Aboensis Math. et Phys.*, 1939, **11**, No. 7, 4; 1939, **11**, No. 14, 3) of which we then became aware (see *J.*, 1949, addendum to p. 1327).

Riebsomer *et al.* (*J. Amer. Chem. Soc.*, 1939, **61**, 3491) attempted the preparation of 5-aryldialuric acids by a variation of the Traube synthesis of pyrimidines, using alcoholic solutions of aryltartronic esters, urea, and sodium ethoxide, but unexpectedly obtained compounds of the type $Ar{\cdot}C_3H_3O_3N$. Identical products were again formed, though in very small amounts, when ammonia was substituted for urea, a result which thus led to their representation as tartronimides (Riebsomer *et al.*, *loc. cit.*). Recognition of Pellizzari's supposed tartronimides as oxazolid-diones makes it evident that the products described by the American authors are similarly constituted, a conclusion supported by the concordance of melting point recorded for the supposed phenyltartronimide (Riebsomer *et al.*, *loc. cit.*) and for 5-phenyloxazolid-2 : 4-dione (III; R = R′ = H) (Traube and Ascher, *Ber.*, 1913, **46**, 2082); this has now been confirmed by a mixed melting point with an authentic specimen synthesised from ethyl mandelate and urea.

Similarly, the compound formed on mild alkaline hydrolysis of the newly prepared 5-*p*-methoxyphenyldialuric acid (I; R = OMe, R′ = H) is indistinguishable from 5-*p*-methoxyphenyloxazolid-2 : 4-dione (III; R = OMe, R′ = H) synthesised from 4-methoxymandelamide and ethyl carbonate in alcoholic sodium ethoxide. The formation of oxazolid-diones from aryltartronic esters does not, however, appear to involve the corresponding dialuric acids as intermediates since the 5-(2 : 4-dimethoxyphenyl)dialuric acid is only very slightly affected by alcoholic sodium ethoxide under the conditions of the Riebsomer reaction.

* Part I, preceding paper.

2 : 4-Dimethoxyphenylglyoxal and 2 : 4-dimethoxymandelonitrile have been prepared in connection with the identification of the 5-(2 : 4-dimethoxyphenyl)oxazolid-dione, but owing to unforeseen difficulties in proceeding to the related mandelic acid or amide it was not possible to complete independent syntheses of the hydrolysis products of the dimethoxyphenyldialuric acid.

Experimental.

5-(2 : 4-Dimethoxyphenyl)dialuric Acid.—A solution of alloxan hydrate (36 g.) in hot water (35 c.c.) was made up to 85 c.c. with concentrated hydrochloric acid and mixed with resorcinol dimethyl ether (36 g.) dissolved in ethanol (150 c.c.). Hydrogen chloride was then passed into the mixture for ½—1 hour, whereupon it became solid owing to deposition of crystalline 5-(2 : 4-*dimethoxyphenyl*)*dialuric acid* (42 g.). This was collected, washed with alcohol, and dissolved in boiling water, from which it crystallised in needles, m. p. 263—264° (decomp.) (Found : C, 51·8; H, 4·3; N, 9·8. $C_{12}H_{12}O_6N_2$ requires C, 51·4; H, 4·3; N, 10·0%). The dialuric acid can also be crystallised from ethanol; it gives a green colour in concentrated sulphuric acid. It was unchanged (recovery 80%) after being heated at 115—120° for 8 hours with sodium ethoxide (3 equivalents) in ethanol, and no oxazolid-dione could be detected.

2 : 4-Dimethoxyphenyltartronic Acid.—A solution of the dimethoxyphenyldialuric acid (12 g.) in 10N-potassium hydroxide (26 c.c.) was evaporated to dryness, with stirring, on a steam-bath. The product was redissolved in water (30 c.c.) and again taken to dryness, the residue then being dissolved in water (30 c.c.) and the solution brought to pH 6·7 by the addition of acetic acid (*ca.* 12 g.). After dilution with alcohol (4 vols.) the solution was left at 0—2° for 48 hours, whereupon a colourless potassium salt (2·2 g., 15%) was precipitated; a further small quantity was deposited on the continued addition of alcohol. The salt (1 g.) was shaken with excess of ethereal hydrogen chloride for 20 minutes, and after filtration the solution was evaporated, the residue of 2 : 4-dimethoxyphenyltartronic acid (0·5 g.), m. p. 128° (effervescence), being dried in a vacuum over phosphoric anhydride. Esterification with diazomethane gave *methyl* 2 : 4-*dimethoxyphenyltartronate*, which crystallised from light petroleum (b. p. 100—120°) in colourless needles, m. p. 95° (Found : C, 54·7; H, 5·5. $C_{13}H_{16}O_7$ requires C, 54·9; H, 5·7%).

2 : 4-Dimethoxymandelic Acid.—A solution of 2 : 4-dimethoxyphenyltartronic acid, or its potassium salt, in hydrochloric acid (6%) was heated on a steam-bath for ½ hour. The product was extracted with ether, and evaporation of the solvent left 2 : 4-*dimethoxymandelic acid* which crystallised from benzene in shining plates, m. p. 130° (Found : C, 57·1; H, 6·0. $C_{10}H_{12}O_5$ requires C, 56·7; H, 5·7%).

5-(2 : 4-Dimethoxyphenyl)oxazolid-2 : 4-dione.—The dimethoxyphenyldialuric acid (40 g.) was dissolved in N-sodium hydroxide (600 c.c.), and the solution heated on a steam-bath for 20 minutes. The clear liquid was then cooled and acidified, and next day the crystalline product (22—23 g., 65—70%) was collected and crystallised from water. The *dimethoxyphenyloxazolid-dione* was thus obtained as clusters of needles, m. p. 179° (Found : C, 56·0; H, 4·6; N, 5·9%; active H, 0·8 atom; *M*, 236. $C_{11}H_{11}O_5N$ requires C, 55·7; H, 4·7; N, 5·9%; active H, 1 atom; *M*, 237). The oxazolid-dione which is sparingly soluble in cold water dissolves readily in aqueous sodium hydroxide and carbonate. It is a strong acid and can be titrated to phenolphthalein with alkalis (N/10) (Found : equiv., 241). The oxazolid-dione gives a green solution in concentrated sulphuric acid. The silver salt precipitated from an aqueous solution of the sodium compound with silver nitrate is readily soluble in aqueous ammonia and in dilute nitric acid. The oxazolid-dione is oxidised by aqueous permanganate to 2 : 4-dimethoxybenzoic acid, m. p. and mixed m. p. 108°.

Methylation of the oxazolid-dione (II; R = R′ = OMe) with ethereal diazomethane gave 5-(2 : 4-*dimethoxyphenyl*)-3-*methyloxazolid*-2 : 4-*dione*, crystallising from aqueous methanol in colourless needles, m. p. 111—112° (Found : C, 57·4; H, 5·4; N, 5·7; OMe, 24·9; NMe, 7·29. $C_{12}H_{13}O_5N$ requires C, 57·4; H, 5·2; N, 5·6; OMe, 24·7; NMe, 11·6%). The *N*-methyl derivative was recovered unchanged after being heated with acetic anhydride for 8 hours.

The solution obtained by heating 5-(2 : 4-dimethoxyphenyl)oxazolid-2 : 4-dione (1 g.) with acetic anhydride (30 c.c.) on a steam-bath for 1 hour was filtered from a small unidentified residue (m. p. 256—260°), evaporated under reduced pressure, and finally dried at 110° over potassium hydroxide. The *acetyl* derivative (0·7 g.), m. p. 124°, when crystallised from alcohol formed needles, m. p. 125° (Found : C, 56·3; H, 4·7; N, 5·1. $C_{13}H_{13}O_6N$ requires C, 55·9; H, 4·7; N, 5·0%). This compound is insoluble in cold aqueous alkalis and its solutions do not form a precipitate with silver nitrate.

5-Phenyloxazolid-2 : 4-dione.—To a solution of sodium (1·25 g.) in dry ethanol (30 c.c.) were added ethyl mandelate (9 g.) and urea (3 g.). After 2 hours' heating under reflux the mixture was evaporated under reduced pressure and the residue dissolved in water (*ca.* 60 c.c.). Acidification of the filtered solution gave the 5-phenyloxazolidione (6·85 g., 77%), m. p. 103—104°, which on recrystallisation from water gave plates, m. p. 107—108°. Traube and Ascher (*Ber.*, 1913, **46**, 2082), who obtained it from 2-imino-5-phenyloxazolid-4-one, give m. p. 108°. The 3-methyl derivative formed by the action of diazomethane, had m. p. 112—113°. Aspelund (*Finska Kem. Medd.*, 1940, **49**, 49) found m. p. 113° for a specimen synthesised from phenylchloroacetyl chloride and *N*-methyl-*N*′-phenylurea.

Repetition of the preparation from ethyl phenyltartronate and urea (Riebsomer *et al.*, *loc. cit.*) gave 5-phenyloxazolid-2 : 4-dione (16%), m. p. 107—108° alone or mixed with a specimen synthesised from ethyl mandelate, and the *N*-methyl derivative had m. p. and mixed m. p. 112—113°. The preparation of ethyl phenyltartronate (Riebsomer, *loc. cit.*) using 1·2 mols. of stannic chloride affords the tartronate, b. p. 154—162°/1 mm., in 28% yield.

5-p-Methoxyphenyldialuric Acid.—A solution (47 c.c.) containing alloxan hydrate (20 g.) in hot water (10 c.c.) and concentrated hydrochloric acid was added to a mixture of anisole (16 g.) and ethanol (100 c.c.), and the whole saturated with hydrogen chloride. The product which separated after 24 hours at room temperature and a further 2 hours' cooling at 0° consisted of the crude p-*methoxyphenyldialuric acid* (11·5 g., 32%), m. p. 230° (decomp.), and when recrystallised from hot water formed needles, m. p. 239° (decomp.) (Found : C, 53·2; H, 4·0; N, 10·9. $C_{11}H_{10}O_4N_2$ requires C, 52·8; H, 4·0; N, 11·2%).

5-p-Methoxyphenyloxazolid-2 : 4-dione.—(i) 5-*p*-Methoxyphenyldialuric acid (5·4 g.) was heated in 2N-sodium hydroxide (34 c.c.) on a steam-bath for 30 minutes. The solution was cooled in ice-water and acidified with concentrated hydrochloric acid until precipitation of the p-*methoxyphenyloxazolid-2 : 4-dione* (2·1 g., 47%) was complete. Recrystallisation from hot water gave colourless plates, m. p. 135—136° (Found : C, 57·9; H, 4·3; N, 7·0. $C_{10}H_9O_4N$ requires C, 57·95; H, 4·4; N, 6·8%). Dissolved in aqueous alkali and treated with potassium permanganate, the dione (0·2 g.) gave, on acidification and treatment with sulphur dioxide, *p*-anisic acid (0·075 g., 50%), m. p. 181—182°.

(ii) (cf. Wallingford, U.S.P. 2,338,220; *Chem. Abs.*, 1944, **38**, 3666). To a solution of sodium (0·4 g.) in ethanol (7 c.c.), ethyl carbonate (3 g.) and an ethanolic solution (40 c.c.) of 4-methoxymandelamide (3 g.) were added and the mixture was heated under reflux for 2 hours. The precipitated sodium salt was collected and dissolved in water, the solution on acidification depositing the 5-*p*-methoxyphenyloxazolid-2 : 4-dione. With a further small amount obtained by concentration of the alcoholic filtrate, shaking with water, and filtration from insoluble 4-methoxymandelamide (0·2 g.) followed by acidification, the yield was 2·15 g. Crystallisation from water gave clusters of plates, m. p. 135—136° alone or mixed with a specimen derived from the dialuric acid.

Methylation of the oxazolid-dione with ethereal diazomethane gave *3-methyl-5-p-methoxyphenyloxazolid-2 : 4-dione*, glistening plates (from alcohol), m. p. 141—142° (Found : C, 59·7; H, 5·2; N, 6·7. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0; N, 6·3%).

2 : 4-Dimethoxyphenylglyoxal.—2 : 4-Dimethoxyacetophenone (Perkin, Robinson, and Turner, *J.*, 1908, **93**, 1108) gives a *semicarbazone* crystallising from ethanol and having m. p. 206° (Found : C, 55·8; H, 6·3; N, 17·5. $C_{11}H_{15}O_4N_3$ requires C, 55·7; H, 6·4; N, 17·7%). The ketone (30 g.) was oxidised in dioxan with selenious acid as described for acetophenone (*Org. Synth.*, **15**, 67). After removal of the solvent under reduced pressure the residue was thrice extracted with hot water (3 × 170 c.c.), but the desired product failed to separate from the aqueous solution (charcoal) even after concentration. It was therefore extracted with chloroform, and the product (30 g.) eventually solidified (m. p. 99°) but was not readily recrystallised.

It was characterised by the *semicarbazone*, light yellow plates, m. p. 205—206°, from ethanol (Found : C, 52·6; H, 5·4; N, 16·6. $C_{11}H_{13}O_4N_3$ requires C, 52·6; H, 5·2; N, 16·7%). A mixed m. p. with dimethoxyacetophenone semicarbazone was *ca.* 186°. The 2 : 4-dimethoxyphenylglyoxal, unlike the isomeric 2 : 6-dimethyl ether (Fuson, McKeever, Rabjohn, and Gray, *J. Amer. Chem. Soc.*, 1943, **65**, 1028), failed to undergo rearrangement in alkaline conditions to the corresponding mandelic acid.

2 : 4-Dimethoxymandelonitrile.—A solution of potassium cyanide (21 g., 4 mols.) in water (55 c.c.), mixed with 2 : 4-dimethoxybenzaldehyde sodium bisulphite compound (21 g., 1 mol.), was cooled in ice-water and shaken with benzene (50 c.c.) until two clear layers were obtained. The benzene solution was then separated, washed with water, and finally treated with anhydrous magnesium sulphate. When completely dry, the filtered solution was diluted with light petroleum to turbidity and left at 0°. After 5 days the crystalline product (5·65 g.) was collected, and a further quantity (2·7 g.) obtained by evaporation of the solution to dryness and crystallisation from benzene–light petroleum. The 2 : 4-*dimethoxymandelonitrile* (8·35 g., 55%), m. p. 65—66°, when recrystallised from light petroleum formed colourless needles, m. p. 66—67° (Found : C, 62·1; H, 6·05; N, 7·2. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·2%). Various attempts to convert the nitrile into derivatives of 2 : 4-dimethoxymandelic acid were unsuccessful. Cold concentrated hydrochloric acid led to a product insoluble in aqueous alkali. Solutions in concentrated sulphuric acid, and in ethereal hydrogen chloride containing an equivalent of alcohol, when poured into water gave nitrogenous products from which, however, no mandelamide was isolated. Reactions between resorcinol dimethyl ether and ethyl mesoxalate (cf. Riebsomer, *loc. cit.*) or ethoxalyl chloride in presence of various catalysts also failed.

THE UNIVERSITY, NOTTINGHAM.

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682. *The Structures of Some Supposed Azetid-2 : 4-diones. Part III. The "Alloxan-5-o-dimethylaminoanil" of Rudy and Cramer, and its Alkali Hydrolysis Product.*

By F. E. King and J. W. Clark-Lewis.

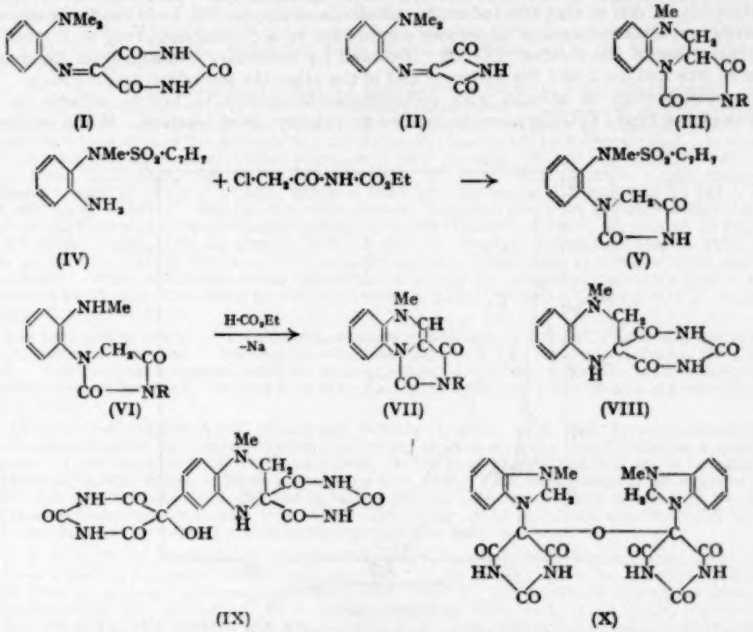
Neither the so-called "alloxan-5-*o*-dimethylaminoanil" nor the compound obtained from it by alkaline hydrolysis contains a dimethylamino-group and hence they cannot have the structures attributed to them by Rudy and Cramer (*Ber.*, 1938, **71**, 1234; 1939, **72**, 227, 728; *Oesterr. Chem.-Ztg.*, 1939, **42**, 329). The secondary product, hitherto regarded as mesoxalimide *o*-dimethylaminoanil, has been identified by synthesis as 1 : 2 : 3 : 4 : 2′ : 4′-hexahydro-2′ : 4′-diketo-4-methylglyoxalino(1′ : 5′-1 : 2)quinoxaline. It follows that the supposed alloxan anil is 1 : 2 : 3 : 4-tetrahydro-4-methylquinoxaline-2-*spiro*-5-(hexahydro-2 : 4 : 6-triketopyrimidine), formed as a result of a unique ring-closure involving a methyl group of the *o*-dimethylamino-substituent.

Condensation of alloxan and *o*-dimethylaminoaniline in alcoholic solution leads to the formation of a compound believed by Rudy and Cramer (*Ber.*, 1938, **71**, 1234; 1939, **72**, 227, 728; *Oesterr. Chem.-Ztg.*, 1939, **42**, 329) to be the anil (I). This product, hereafter called A, is transformed by boiling 30% aqueous sodium or potassium hydroxide into a crystalline derivative B to which these authors have assigned the highly problematical mesoxalimide anil structure (II). Analyses, a colour reaction with hydrogen peroxide–hydrochloric acid said to be specific for the *o*-dimethylaminoanil grouping, and, in the case of B, a molecular-weight determination, are quoted as evidence for the proposed formulæ, and similar expressions have been used to represent the corresponding products derived from 2-dimethylamino-4 : 5-dimethylaniline. Nevertheless, the general properties of the compound B as recorded by Rudy and Cramer are incompatible with the structure (II). The supposed mesoxalimide anil is, for example, unaffected when heated with 50% aqueous sodium hydroxide or concentrated hydrochloric acid. This high degree of acid stability, which is characteristic too of the parent compound A, is unparallelled in the series of Schiff's bases, and Rudy and Cramer have consequently attributed the exceptional properties of the supposed anils A and B to the influence of the *o*-dimethylamino-substituent.

In view of these anomalous observations a further investigation of the problem has been undertaken. First, the postulated effect of the *o*-dimethylamino-group on anil stability was examined by reference to benzylidene-*o*-dimethylaminoaniline, whereupon it was observed that this new derivative, in contrast to the compounds A and B, exhibited the usual acid lability of the normal Schiff's base. Moreover, alloxan-5-*p*-dimethylaminoanil (Piloty and Finckh, *Annalen*, 1904, **333**, 37), a blue-black microcrystalline powder, also readily undergoes hydrolysis as is apparent from the immediate decolorisation of its deep blue-violet aqueous alcoholic solutions on the addition of dilute acid. Its isomer A, on the other hand, is light yellow, and the supposed anil B together with the *N*-methyl derivative prepared from it by the action of diazomethane are colourless. These marked differences between the prope ties of the authentic anil and the compounds A and B are quantitatively expressed by their respective ultra-violet absorption spectra (see figure) and render improbable the structures (I) and (II) proposed by Rudy and Cramer.

Evidence decisively excluding the anil structure (II) was obtained from a Herzig–Meyer analysis of the derivative B which gave a value indicative of the presence of only one *N*-methyl group in the molecule. It thus became apparent that in addition to the primary amino-group the *o*-dimethylamino-substituent of the constituent base had at one stage or the other reacted with the alloxan moiety. This further condensation we supposed to have taken place at the former alloxan-5-carbonyl group thus leading to a hydroquinoxaline system, since cyclisation at any other position would imply the formation of a ring larger than 6-membered. On this hypothesis it was possible to suggest for the alkali hydrolysis product B a new constitution (III; R = H) containing the hitherto unknown quinoxalino–hydantoin skeleton, which because of the ease of formation and general stability of the hydantoin ring afforded a more convincing interpretation of the properties of compound B than the structure (II) proposed by Rudy and Cramer.

This new structure was confirmed by synthesis of 1 : 2 : 3 : 4 : 2′ : 4′-hexahydro-2′ : 4′-diketo-4 : 3′-dimethylglyoxalino(1′ : 5′-1 : 2)quinoxaline (III; R = Me), identical with the *N*-methyl derivative formerly obtained by Rudy and Cramer from the product B. A suitably substituted hydantoin was first prepared according to the general method of Frerichs and Breustedt (*J. pr. Chem.*, 1902, **66**, 231) by heating *N*-*o*-aminophenyl-*N*-methyltoluene-*p*-sulphonamide (IV) with chloroacetylurethane, of which an improved preparation is described. The resulting 1-*o*-(*N*-methyltoluene-*p*′-sulphonamido)phenylhydantoin (V) was hydrolysed by a mixture of acetic and sulphuric acids at 100° to 1-*o*-methylaminophenylhydantoin (VI; R = H), which



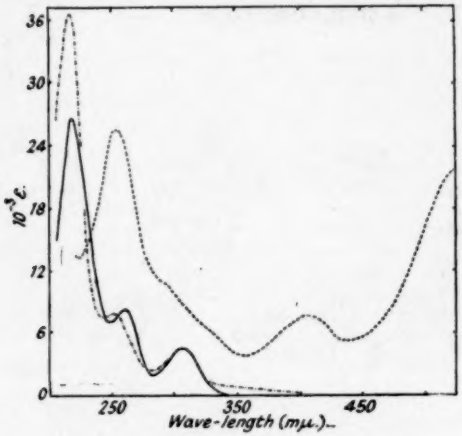
on methylation with diazomethane gave the 3-methylhydantoin (VI; R = Me) further characterised by its acetyl derivative. The intermediate (VI; R = Me) was alternatively obtained when the sulphonamidophenylhydantoin (V) was first methylated with methyl iodide–potassium carbonate and the methyl derivative then hydrolysed. The product (VI; R = Me) was then treated with powdered sodium in excess of ethyl formate, but instead of the expected intermediate sodium enolate of the 2-formylhydantoin, direct formation of the brilliant orange-yellow tetrahydrodiketoglyoxalinoquinoxaline (VII; R = Me) occurred. A similar condensation with ethyl acetate gave the 3-methyl homologue of (VII; R = Me), but the hydantoin (VI; R = Me) failed to react with ethyl benzoate.

Some difficulty was encountered in attempted catalytic reduction of the tetrahydro-compound (VII; R = Me), but tin and hydrochloric acid yielded the hexahydro-compound (III; R = Me) identical with the *N*-methyl derivative of compound B. Subsequently, the condensation of 1-*o*-methylaminophenylhydantoin (VI; R = H) and ethyl formate was effected, though less successfully than with the 3′-methyl derivative; reduction of the product yielded compound B, hitherto formulated as (II). It follows, furthermore, that a constitution analogous to (VII; R = H) may be assigned to the homologue of B obtained by alkaline hydrolysis of the so-called alloxan-2-dimethylamino-4 : 5-dimethylanil (Rudy and Cramer, *loc. cit.*).

It was then apparent that the primary condensation product also might contain the quinoxaline system. This view was supported by the resemblance of the ultra-violet absorption spectra of the two compounds and was largely confirmed when it was shown that compound A

possessed only one *N*-methyl group instead of the two required by Rudy and Cramer's expression (I). Moreover, in the dimethyl derivative which may be prepared from A by the action of diazomethane (Rudy and Cramer, *loc. cit.*), the existence of a replaceable hydrogen atom has now been demonstrated both by the Zerewitinoff method and by the formation of a monoacetyl derivative. It is therefore concluded that the supposed anil (I) is in fact a spiran (VIII), the active group of the dimethyl derivative being the basic >NH of the tetrahydroquinoxaline ring; similar constitutions may be presumed for the compounds prepared from 2-dimethylamino-4-methyl-, -5-methyl-, and -4 : 5-dimethyl-aniline. The alkali degradation leading to (III; R = H) is thus analogous to the formation described in Part II of oxazolid-diones from dialuric acids, which is also effected under alkaline conditions. In both reactions the hexahydrotriketopyrimidine nucleus undergoes contraction to a 5-membered ring as a result of a preliminary loss of the residue $^{-}CO{\cdot}NH^{-}$, followed by subsidiary condensations involving in one series (the dialuric acids) the hydroxyl and in the other the secondary amino-group.

The condensation of alloxan with *o*-dimethylaminoanilines in boiling ethanol to form products of the type (VIII) appears to involve an entirely novel reaction. When assisted by



Absorption curves.

———— 1 : 2 : 3 : 4 : 2′ : 4′-*Hexahydro*-2′ : 4′-*diketo*-4 : 3′-*dimethylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline* (III; R = Me) *in* 95% *ethanol.*
– – – – – – – *Alloxan*-5-p-*dimethylaminoanil in methanol.*
— · — · — 1 : 2 : 3 : 4-*Tetrahydro*-4-*methylquinoxaline*-2-spiro-5-(*hexahydro*-2 : 4 : 6-*triketopyrimidine*) (VIII) *in methanol.*

a small quantity of hydrochloric acid the condensation will occur even at room temperature. Under no conditions, however, does the yield exceed 25%, and Rudy and Cramer have reported the isolation of two by-products. One of these, which can also be obtained from (VIII) by the further action of alloxan, is evidently a dialuric acid, to which Rudy and Cramer have attributed a structure based on the expression (I). On the new formulation of A this becomes (IX), the location of the second pyrimidine nucleus *para* to the quinoxaline-*N*-methyl group being substantiated by data already published (Rudy and Cramer, *loc. cit.*). The third product is believed by the German authors to have the formula (X). They have recorded that its oxidation with hydrogen peroxide in acetic acid gives 1-methylbenziminazole, but the remaining evidence for (X) is unconvincing, and pending a reinvestigation of this substance we reserve further comment on its structure.

Details are given in the Experimental section of intermediates prepared in other uncompleted syntheses of the glyoxalinoquinoxaline (III). *N*-*o*-Nitrophenylglycine, obtained as the ethyl ester from *o*-nitroaniline and ethyl bromoacetate, failed to give 1-*o*-nitrophenylhydantoin when heated with urea, and various other standard hydantoin syntheses were also unsuccessful, evidently owing to the influence of the *o*-nitro-group. Attempts were made to prepare an

o-nitro-derivative of 1-(3 : 4-dimethylphenyl)hydantoin, but the principal product was a dinitro-compound and only traces of a mononitrated substance were isolated. In other experiments connected with this problem it was observed that on heating *N*-methyl-*o*-nitroaniline with ethyl bromo-pyruvate or -oxaloacetate, 4-bromo-*N*-methyl-2-nitroaniline is obtained.

Experimental.

Benzylidene-o-dimethylaminoaniline.—o-Dimethylaminoaniline was obtained by hydrogenation over Raney nickel of *NN*-dimethyl-*o*-nitroaniline (prepared from *o*-chloronitrobenzene as described by Campbell, *J. Amer. Chem. Soc.*, 1949, **71**, 740). With benzaldehyde the amine gave *benzylidene-o-dimethylaminoaniline* as a viscous yellow oil (Found : C, 79·8; H, 7·05; N, 12·5. $C_{15}H_{16}N_2$ requires C, 80·3; H, 7·2; N, 12·5%). Light absorption in ethanol (95%) : max. at 248 mμ (ε = 16,550), min. at 231 mμ (ε = 13,100). When cold dilute mineral acid was added to the anil, benzaldehyde was immediately liberated.

1 : 2 : 3 : 4-*Tetrahydro-4-methylquinoxaline*-2-spiro-5-(*hexahydro*-2 : 4 : 6-*triketopyrimidine*) (VIII).—This *spiran* was obtained in 15% yield from *o*-dimethylaminoaniline and alloxan hydrate by Rudy and Cramer's method (*loc. cit.*) and in 19% yield by keeping the reactants in aqueous ethanol at room temperature for 3 days in the presence of a few drops of concentrated hydrochloric acid. It crystallised from aqueous pyridine in small, yellow plates, m. p. 250° (decomp.) (Found : C, 55·0; H, 5·0; N, 20·9; NMe, 10·4. $C_{12}H_{13}O_3N_4$ requires C, 55·4; H, 4·7; N, 21·5; NMe, 11·2%). Light absorption in methanol : max. at 217 (ε = 36,450), 250 (ε = 7520) and 306 mμ (ε = 4500); min. at 242 (ε = 7250) and 283 mμ (ε = 2275). Methylation with ethereal diazomethane gave the *di-N-methyl* derivative, crystallising from ethanol in pale yellow prisms, m. p. 194° (Found : C, 59·0; H, 5·4; N, 19·6%; active H, 0·8 atom. $C_{14}H_{16}O_3N_4$ requires C, 58·3; H, 5·6; N, 19·4%); light absorption in 95% ethanol : max. at 218 (ε = 40,000), 250 (ε = 7710), and 306 mμ (ε = 5030); min. at 246 (ε = 7400) and 282 mμ (ε = 2280). When boiled with acetic anhydride for 1 hour the *N*-methyl derivative yielded an *acetyl* derivative which crystallised from ethanol in needles, m. p. 288° (Found : C, 58·4; H, 5·2. $C_{16}H_{18}O_4N_4$ requires C, 58·2; H, 5·5%).

The pale yellow colour of an alcoholic solution of the *spiro*-compound (VIII) was not discharged by shaking with zinc dust or by heating with magnesium (cf. Zechmeister and Truka, *Ber.*, 1930, **63**, 2883). The compound resisted catalytic hydrogenation over Adams's platinic oxide catalyst at room temperature and pressure. It gave a violet colour with hydrogen peroxide and concentrated hydrochloric acid.

Alloxan-5-p-*dimethylaminoanil* (Piloty and Finckh, *Annalen*, 1904, **333**, 37).—Condensation of *p*-dimethylaminoaniline and alloxan hydrate in boiling alcohol gave the Schiff's base as a nearly black powder. Light absorption in methanol : max. at 256 (ε = 26,400) and 405 mμ (ε = 7550); min. at 225 (ε = 13,240), 355 (ε = 3820), and 440 mμ (ε = 5220). The blue colour of an aqueous solution of the anil was immediately discharged by dilute mineral acid and was not restored on the dropwise addition of dilute aqueous sodium hydroxide. The colour of the liquid was also destroyed by shaking with zinc dust and by heating a methanolic solution with magnesium.

1 : 2 : 3 : 4 : 2′ : 4′-*Hexahydro*-2′ : 4′-*diketo*-4-*methylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline* (III; R = H).—When boiled with aqueous sodium hydroxide (30%) (cf. Rudy and Cramer, *loc. cit.*) the *spiro*-compound (VIII) (0·5 g.) gave the *quinoxalinohydantoin* (III; R = H) (0·2 g.) which crystallised from ethanol in needles, m. p. 240° (Found : C, 61·0; H, 5·2; N, 18·8; NMe, 14·1. $C_{11}H_{11}O_3N_3$ requires C, 60·8; H, 5·1; N, 19·3; NMe, 13·4%), and was coloured violet by a hydrogen peroxide–concentrated hydrochloric acid mixture.

Methylation with ethereal diazomethane formed 1 : 2 : 3 : 4 : 2′ : 4′-*hexahydro*-2′ : 4′-*diketo*-4 : 3′-*dimethylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline* (III; R = Me) which separated from ethanol in prisms, m. p. 154° (Found : N, 18·3. $C_{13}H_{15}O_3N_3$ requires N, 18·2%). Light absorption in ethanol (95%) : max. at 218 (ε = 26,500), 260 (ε = 8600), and 307 mμ (ε = 4700); min. at 248 (ε = 7590) and 284 mμ (ε = 1930). The picrate, which crystallised from ethanol in chocolate-brown needles, m. p. 133°, was unstable.

N-o-*Aminophenyl*-N-*methyltoluene*-p-*sulphonamide* (IV).—A suspension of powdered *N*-methyltoluene-*p*-sulphon-*o*′-nitroanilide (85 g.) (Usherwood and Whiteley, *J.*, 1923, 1084; Phillips, *J.*, 1929, 2820) in ethanol (300 ml.) was hydrogenated at room temp./6 atm. over Raney nickel. The product was dissolved by warming and the catalyst removed by filtration through kieselguhr, the filtrate depositing the *amide* (IV) as needles or prisms, m. p. 107—108° (62 g., 80%), soluble in dilute acids and sparingly soluble in water (Found : C, 61·0; H, 5·2; N, 10·2. $C_{14}H_{16}O_3N_2S$ requires C, 60·8; H, 5·8; N, 10·15%). A further quantity (10 g., total 94%) crystallised when the filtrate was concentrated.

Chloroacetylurethane.—Urethane (50 g.) was added to ether (300 c.c.) containing sodium wire (13 g.), and the mixture heated on a steam-bath until formation of the sodium salt was complete (5—6 hours). Ethyl chloroacetate (68·5 g.) was added to the cold suspension, and the mixture heated on a steam-bath for 5 hours and then left at room temperature for 14 hours. Ice and concentrated hydrochloric acid (56·5 c.c.) were then added alternately, and the ice-cold mixture shaken to complete decomposition of the sodium salt. The crystalline solid (72 g.) was collected and the remainder (5 g.) isolated by extraction of the aqueous layer with ether. Crystallisation from ethyl acetate gave chloroacetylurethane (70 g., 75%), m. p. 128—129°, also crystallising (in plates) from water, but with poor recovery (*ca.* 50%) presumably owing to hydrolysis (cf. Ruhemann and Priestley, *J.*, 1909, **95**, 453).

1-o-(*N-Methyltoluene*-p′-*sulphonamido*)*phenylhydantoin* (V).—A mixture of the amine (IV) (62 g., 1 mol.), chloroacetylurethane (37 g., 1 mol.), and dimethylaniline (27·2 g., 1 mol.) was heated at 120—

130° for 6 hours. The brownish-red product was treated with ether containing a little alcohol, and the solid residue washed in turn with ether, water, dilute hydrochloric acid, ethanol, and ether. Recrystallisation from ethanol gave the *hydantoin* (V) (44 g., 45%) as colourless prisms, m. p. 268—270° (Found: C, 57·0; H, 4·7; N, 11·5. $C_{17}H_{17}O_4N_3S$ requires C, 56·8; H, 4·8; N, 11·7%). The hydantoin is very sparingly soluble in hot water and in ethanol and only slightly soluble in aqueous sodium hydroxide. It was largely unchanged after being kept for 14 hours with sulphuric acid (90%) at room temperature, being then recovered when the mixture was poured into ice-water.

The use of alcohol in the above reaction, as in the experiments of Frerichs and Breustedt (*loc. cit.*), gave a poor yield of the hydantoin (V) (14%) together with N-o-(N-*methyltoluene-p'-sulphonamido*)-*phenylglycine ethyl ester* (8·5%), the latter being more soluble in alcohol and separating from it in prisms, m. p. 150° (Found: C, 59·5; H, 5·7; N, 7·7. $C_{18}H_{22}O_4N_2S$ requires C, 59·7; H, 6·1; N, 7·7%). When a mixture of the amine (IV) (2 mols.) and chloroacetylurethane (1 mol.) was kept at 100° for 18 hours and the product triturated and left with alcohol, a solid, m. p. 145—150°, was obtained consisting largely of the substituted glycine ester, m. p. 150° (65%) which was removed by a little hot ethanol leaving a residue of the hydantoin (V) (10%). After precipitation of excess of amine (IV) from the original alcoholic solution by ether, evaporation and sublimation of the residue gave ethyl carbamate, m. p. 50°.

1-o-*Methylaminophenylhydantoin* (VI; R = H).—The hydantoin (V) (3 g.) was heated for 1 hour on a steam-bath with 6 c.c. of a solution prepared by mixing acetic acid (41 c.c.) and concentrated sulphuric acid (92·5 c.c.). Recrystallisation, from ethanol, of the precipitate formed by pouring the solution into ice-water gave 1-o-*methylaminophenylhydantoin* (VI; R = H) (1·45 g., 85%) in plates, m. p. 224—226° (Found: C, 58·1; H, 5·4; N, 20·7. $C_{10}H_{11}O_2N_3$ requires C, 58·5; H, 5·4; N, 20·5%). The hydantoin is soluble in dilute mineral acids and in hot ethanol, and sparingly soluble in water.

3-*Methyl*-1-o-*methylaminophenylhydantoin* (VI; R = Me).—(i) Methylation of (VI; R = H) with ethereal diazomethane for 18 hours gave 3-*methyl*-1-o-*methylaminophenylhydantoin* (VI; R = Me), crystallising from ethanol in prisms, m. p. 153—154° (Found: C, 60·3; H, 5·9; N, 19·0. $C_{11}H_{13}O_2N_3$ requires C, 60·3; H, 6·0; N, 19·2%), and sparingly soluble in water, but soluble in dilute mineral acids and in organic solvents.

(ii) A mixture of 1-o-(*N*-methyltoluene-*p'*-sulphonamido)phenylhydantoin (V) (8·4 g.), acetone (50 c.c.), methyl iodide (23 g.), and anhydrous potassium carbonate (30 g.) was heated under reflux for 36 hours. The solvent was removed under reduced pressure and, after being washed with water to remove inorganic salts, the residual clear gum (*ca.* 8 g.) was crystallised from benzene–light petroleum. The resulting 3-*methyl*-1-o-(N-*methyltoluene*-p'-*sulphonamido*)*phenylhydantoin* formed plates, m. p. 134—135° (Found: N, 11·0. $C_{18}H_{19}O_4N_3S$ requires N, 11·3%). Hydrolysis with acetic–sulphuric acid mixture as in the preparation of (VI; R = H) gave 3-methyl-1-o-methylaminophenylhydantoin (VI; R = Me) (60%), m. p. 153—154°. With acetic anhydride the product (1 g.) afforded 3-*methyl*-1-o-N-*methylacetamidophenylhydantoin* (0·9 g., 75%), prisms (from ethanol), m. p. 187—188° (Found: N, 16·5; $C_{13}H_{15}O_3N_3$ requires N, 16·1%).

1 : 4 : 2′ : 4′-*Tetrahydro*-2′ : 4′-*diketo*-4 : 3′-*dimethylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline* (VII; R = Me).—A mixture of 3-methyl-1-o-methylaminophenylhydantoin (VI; R = Me) (4 g., 1 mol.) and ethyl formate (17·5 g.) was heated with powdered sodium (0·4 g., 1·05 equiv.) on a steam-bath for 2 hours. A brisk evolution of hydrogen occurred and the solution deposited an orange-yellow solid (3·5 g., 85%), which was collected after 12 hours at room temperature. Crystallisation of the solid from hot ethanol, after washing with dilute hydrochloric acid, water, and alcohol, gave 1 : 4 : 2′ : 4′-*tetrahydro*-2′ : 4′-*diketo*-4 : 3′-*dimethylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline* (VII; R = Me) as lustrous orange-yellow long hair-like needles, m. p. 260° (Found: C, 62·9; H, 4·8; N, 18·2. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8; N, 18·3%). The glyoxalinoquinoxaline is slightly soluble in dilute mineral acids and readily soluble in acetic acid. It gives a violet colour with nitric acid, but is unaffected by hydrogen peroxide–hydrochloric acid. The compound could not be reduced by sodium and boiling ethanol or catalytically although slowly undergoing partial hydrogenation at N.T.P. over platinic oxide.

Reduction of 1 : 4 : 2′ : 4′-*Tetrahydro*-2′ : 4′-*diketo*-4 : 3′-*dimethylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline*.—A solution of the glyoxalinoquinoxaline (VII; R = Me) (1·4 g.) in acetic acid (20 c.c.) was mixed with concentrated hydrochloric acid (100 c.c.), and heated on a steam-bath with the gradual addition of granulated tin (25 g.). When reduction was complete (3 hours), the solution was cooled and filtered, and the filtrate cooled in ice-water and strongly basified with aqueous sodium hydroxide (40%). Crystallisation of the organic precipitate from the minimum quantity of hot ethanol gave 1 : 2 : 3 : 4 : 2′ : 4′-*hexahydro*-2′ : 4′-*diketo*-4 : 3′-*dimethylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline* (III; R = Me) (0·664 g., 47%) as colourless prisms, m. p. 154° alone or mixed with the product obtained by the method of Rudy and Cramer (Found: C, 62·1; H, 5·5; N, 18·2. $C_{12}H_{13}O_2N_3$ requires C, 62·3; H, 5·7; N, 18·2%). The *picrate* crystallised in chocolate-brown needles (from ethanol), m. p. 133° (Found: C, 46·8; H, 3·6; N, 18·1. $C_{12}H_{13}O_2N_3,C_6H_3O_7N_3$ requires C, 47·0; H, 3·5; N, 18·3%). The compound gave a violet colour with hydrogen peroxide–concentrated hydrochloric acid and with sulphuric acid containing nitric acid.

1 : 4 : 2′ : 4′-*Tetrahydro*-2′ : 4′-*diketo*-4-*methylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline* (VII; R = H).—A mixture of 1-o-methylaminophenylhydantoin (VI; R = H) (1·7 g., 1 mol.), ethyl formate (15 c.c.), and powdered sodium (0·4 g., 2·1 equivs.) was heated on a steam-bath for 1 hour and then left at room temperature for 14 hours. Neutralisation with aqueous acetic acid gave 1 : 4 : 2′ : 4′-*tetrahydro*-2′ : 4′-*diketo*-4-*methylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline* (VII; R = H) (0·5 g., 28%) which crystallised from ethanol in yellow needles, m. p. 270° (Found: C, 60·9; H, 4·8; N, 19·8. $C_{11}H_9O_2N_3$ requires C, 61·4; H, 4·2; N, 19·5%). Unused hydantoin (VI; R = H) (0·75 g., 44%), m. p. 226°, was recovered by chloroform extraction of the original aqueous solution.

Reduction of the compound (VII; R = H) with tin and hydrochloric acid, as for the homologue (VII; R = Me), removal of the tin as sulphide, and neutralisation with aqueous ammonia gave

1 : 2 : 3 : 4 : 2′ : 4′-hexahydro-2′ : 4′-diketo-4-methylglyoxalino(1′ : 5′-1 : 2)quinoxaline (III; R = H) (*ca.* 0·1 g.), m. p. 239°, identical with that obtained by the method of Rudy and Cramer (*loc. cit.*).

1 : 4 : 2′ : 4′-*Tetrahydro*-2′ : 4′-*diketo*-3 : 4 : 3′-*trimethylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline*.—A mixture of 3-methyl-1-*o*-methylaminophenylhydantoin (VI; R = Me) (2 g., 1 mol.), ethyl acetate (20 c.c.), and powdered sodium (0·4 g., 1·9 equivs.) was heated on a steam-bath for 5 hours. The excess of ethyl acetate was removed under reduced pressure and water was added, the yellow solid which consisted of **1 : 4 : 2′ : 4′-*tetrahydro*-2′ : 4′-*diketo*-3 : 4 : 3′-*trimethylglyoxalino*(1′ : 5′-1 : 2)*quinoxaline*** crystallising from ethanol in small yellow needles, m. p. 190—191° (Found: C, 64·6; H, 5·7; N, 16·9. $C_{13}H_{13}O_3N_3$ requires C, 64·2; H, 5·4; N, 17·3%). 3-Methyl-1-*o*-methylaminophenylhydantoin (0·9 g., 45%) was recovered from the filtrate by extraction with chloroform. When (VI; R = Me) was treated in a similar manner with ethyl benzoate and sodium (1 equiv.) no reaction took place.

N-*o*-*Nitrophenylglycine Ethyl Ester*.—A mixture of ethyl bromoacetate (62 g., 1 mol.) and *o*-nitroaniline (103 g., 2 mols.) was heated in an oil bath at 120—135° for 4½ hours, and then diluted with ether and filtered from *o*-nitroaniline hydrobromide (52 g.). The filtrate was evaporated under reduced pressure, crystallisation of the residue from ethanol (*ca.* 150 ml.) giving N-*o*-*nitrophenylglycine ethyl ester* (50 g., 60%) as long yellow needles, m. p. 77—78°, raised to 80° by recrystallisation from ethanol (Found: C, 53·5; H, 5·3; N, 13·1. $C_{10}H_{12}O_4N_2$ requires C, 53·6; H, 5·4; N, 12·5%). The ester failed to react when heated with ethyl chloroformate alone or in the presence of pyridine, 85% being recovered. It was not hydrolysed after several hours by boiling aqueous or alcoholic alkali, but evaporation with concentrated hydrochloric acid gave *N*-*o*-nitrophenylglycine (90%), orange prisms, m. p. 199°, a method of preparation superior to that of Plöchl (*Ber.*, 1886, **19**, 7).

Attempts to prepare 1-*o*-nitrophenylhydantoin from *N*-*o*-nitrophenylglycine or its ester by standard methods were unsuccessful. Heating chloroacetylurethane (1 mol.) with *o*-nitroaniline (2 mols.) led to *s*-di-*o*-nitrophenylurea (8%), m. p. 223—224°.

N-**3 : 4**-*Dimethylphenylglycine Ether Ester*.—A mixture of **3 : 4**-dimethylaniline (43 g., 2 mols.) and ethyl chloroacetate (20 g., 1 mol.) was heated at 100° for 1 hour. The solid was treated with hot water and the oily product extracted with ether and washed with 2N-hydrochloric acid. Removal of the ether and crystallisation of the residue from light petroleum gave N-**3 : 4**-*dimethylphenylglycine ethyl ester* (23·1 g., 67·5%), as prisms, m. p. 49—50°, or plates from aqueous ethanol (Found: N, 6·9. $C_{12}H_{17}O_2N$ requires N, 6·8%).

1-(**3 : 4**-*Dimethylphenyl*)*hydantoin*.—Heating **3 : 4**-dimethylaniline (21·2 g., 2 mols.) with chloroacetylurethane (14·5 g., 1 mol.) (cf. Frerichs and Breustedt, *loc. cit.*) gave 1-(**3 : 4**-*dimethylphenyl*)*hydantoin* (12 g., 70%), which crystallised from ethanol in long needles, m. p. 206—207° (Found: C, 65·2; H, 6·1; N, 14·3. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9; N, 13·7%). It was also obtained by heating *N*-(**3 : 4**-dimethylphenyl)glycine ester with urea at 150—160° (cf. Schwebel, *Ber.*, 1877, **10**, 2048).

Methylation of the hydantoin (10·7 g.) with methyl iodide and potassium carbonate in acetone gave 1-(**3 : 4**-*dimethylphenyl*)-3-*methylhydantoin* (9 g., 79%), needles (from ethanol), m. p. 169—170° (Found: C, 65·5; H, 6·1; N, 12·8. $C_{12}H_{14}O_2N_2$ requires C, 66·0; H, 6·5; N, 12·8%). An identical product was obtained by methylation with ethereal diazomethane. Treatment of the 1-(**3 : 4**-dimethylphenyl)-3-methylhydantoin with concentrated nitric–sulphuric acids for 10 minutes at 0° gave a *dinitro*-derivative (34%) which crystallised from ethanol in pale yellow prisms, m. p. 226°, and was also obtained by nitration with sulphuric acid containing potassium nitrate (1 mol.) (Found: C, 47·0; H, 4·0; N, 18·9. $C_{12}H_{12}O_6N_4$ requires C, 46·8; H, 3·9; N, 18·3%). Nitration of the methylated hydantoin (0·5 g.) with nitric acid (1 c.c.) in glacial acetic acid (9 c.c.) at room temperature for 14 hours yielded a *mononitro*-derivative crystallising from ethanol in pale yellow prisms (0·067 g., 10%), m. p. 130—132° (Found: C, 55·0; H, 4·8; N, 16·0. $C_{12}H_{13}O_4N_3$ requires C, 54·8; H, 5·0; N, 16·0%).

Reaction of o-*Nitromethylaniline with Ethyl Bromo-oxaloacetate and Ethyl Bromopyruvate*.—*o*-Nitromethylaniline (7·5 g.) and ethyl bromo-oxaloacetate (13·2 g.) were heated together for 4 hours at 130—135° and then added to light petroleum (100 c.c.; b. p. 100—120°). Crystallisation of the solid (6·15 g., 54%) from light petroleum (b. p. 60—80°) gave orange prisms of 4-bromo-2-nitromethylaniline (5 g.), m. p. 93—94°, raised by two crystallisations to 99—100° undepressed by an authentic specimen (Found: C, 37·0; H, 2·7; N, 12·3. Calc. for $C_7H_7O_2N_2Br$: C, 36·4; H, 3·0; N, 12·3%). Heating *o*-nitromethylaniline with ethyl bromopyruvate at 120—130° for 4 hours gave 4-bromo-2-nitromethylaniline (35%) and a dark tar. When the reactants were heated in pyridine no bromonitroaniline was obtained and *o*-nitromethylaniline (80%) was recovered.

THE UNIVERSITY, NOTTINGHAM.

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683. *Pressure–Volume–Temperature Relations in Liquids and Liquid Mixtures. Part I. The Compression of* n-*Hexane,* n-*Heptane,* n-*Octane, and of their Binary and Ternary Mixtures, up to* 5000 *Atmospheres.*

By H. E. Eduljee, D. M. Newitt, and K. E. Weale.

The compression of *n*-hexane, *n*-heptane, *n*-octane, and of binary and ternary mixtures of these hydrocarbons has been determined up to 5000 atmospheres, and at 0°, 25°, 40°, and 60°. The isotherms are expressed in the form of the Tait equation.

The energy–volume coefficients, $(\partial E/\partial V)_T$ and the pressure coefficients, $(\partial P/\partial T)_V$, are found to be pure volume functions, and at all the temperatures and pressures employed the hydrocarbons mix without expansion or contraction in volume.

Measurements of the decrease in volume undergone by liquids at high pressures are an important source of information about the intermolecular forces, and contribute towards a general theory of the liquid state. The first systematic study was made by Amagat (*Ann. Chim. Phys.*, 1893, **29**, 68, 505) on twelve organic liquids up to 3000 atmospheres and in the range 0—200°. Bridgman ("The Physics of High Pressure," 2nd edn., 1949) developed new experimental methods by which Amagat's results were repeated and extended to 12,000 kg./cm.², between 20° and 80°. Bridgman (*op. cit.*; see also *Proc. Amer. Acad. Arts Sci.*, 1949, **77**, 115—146) has measured the volume decrements of a large number of other liquids to 12,000 kg./cm.², and in many cases to 40,000 or 50,000 kg./cm.², but generally not at a sufficient number of different temperatures to enable detailed thermodynamic analysis of his results to be made.

Gibson and his co-workers (*J. Physical Chem.*, 1939, **43**, 207; *J. Amer. Chem. Soc.*, 1938, **60**, 511, and subsequent papers to 1941) have obtained accurate data for eight liquids and some liquid mixtures, at pressures up to 1000 bars. These authors have consistently used the Tait equation to represent their pressure–volume isotherms, and have calculated various functions, such as the energy–volume coefficient and the pressure coefficient for the liquids. The general use of three different units of pressure (1 normal atmosphere = 1·0133 bars = 1·0322 kg./cm.²) is an obstacle to the exact comparison of results from different laboratories, but this may be done from the pressure–volume curves, or by calculation where the Tait constants have been evaluated.

This paper presents the results of volume measurements on *n*-hexane, *n*-heptane, *n*-octane, and mixtures of these hydrocarbons, up to 5000 atmospheres, which was the maximum pressure with the apparatus available, and at 0°, 25°, 40°, and 60°.

Experimental.

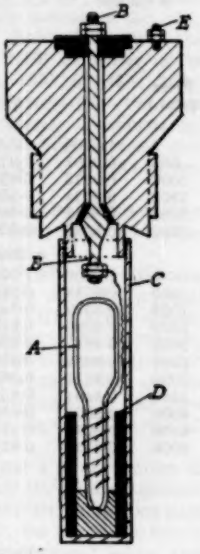
The general arrangement of the high-pressure apparatus has been described previously (see *J.*, 1938, 784, Fig. 1). The pressure vessel is a thick-walled steel cylinder, closed at the top by a steel screw plug seating on a lens ring, and immersed in a thermostat bath. Pressure is generated by a hand pump and transmitted through an intensifier to the bottom of the vessel along a steel pipe-line.

The liquid hydrocarbon is contained in a glass tube, *A*, of the form shown in Fig. 1. The tubes used were of Jena Red Line or Pyrex glass and were carefully annealed. The bulb is of approximately 8 mm. internal diameter, and the ratio of the volume of the bulb to that of the stem is about 4 : 1. A series of contacts of fine platinum wire (diameter 0·005 inch) are sealed into the tube, so that their ends lie along the central axis and point downwards to make clean and sharp contact with the mercury. A length of silk-covered constantan resistance wire (20 ohms per yard) is soldered to the lowest platinum contact and wound spirally round the tube, the other contacts being soldered to bared sections. The upper end of the resistance wire is attached to the lower end of a steel electrode, *B*, which is insulated from the screw plug and passes upward through it to an insulted terminal on its upper face. A cylindrical steel holder, *C*, screws on to the base of the plug and surrounds the glass tube. The holder contains mercury which seals the open end of the stem. Holes in the wall of the holder ensure pressure equalisation inside and out, and the thin-walled ebonite cylinder, *D*, prevents the contacts from accidentally touching the holder walls. Externally the electrical circuit is made from the electrode terminal through a milliammeter and two-volt accumulator to the screw plug at *E*, and thus to the mercury in the holder. When the plug has been tightened into position in the vessel, the glass tube and the mercury holder are immersed in the pressure transmitting fluid—an 80% paraffin oil–20% liquid paraffin mixture. With increasing pressure the mercury rises in the stem, successively cutting out parts of the resistance of the constantan wire and causing abrupt increases in the milliammeter reading.

Preliminary experiments, using a tube open at both ends, established that with rising and falling mercury columns the contacts were made sharply and reproducibly, and did not depend on the nature of the liquid above the mercury. The glass tubes were calibrated by weighing when empty, when full of mercury, and when containing sufficient mercury just to touch each contact in turn. In use the tubes were frequently recalibrated, satisfactory agreement being obtained.

A weighed tube (containing a globule of mercury to seal the bottom of the stem on inversion, and during transfer to the mercury holder) was filled with liquid, inverted quickly, stood in a mercury-containing crucible of known weight, and reweighed after any overflow liquid had evaporated. After a little practice, this operation could be performed without introducing air bubbles, and with the minimum of overflow. The tube was transferred to the steel mercury holder, which was attached to the plug and screwed into position in the pressure vessel. The thermostat bath was then heated or cooled, about 5 hours being allowed for the apparatus to attain a steady temperature, which was controlled to $\pm 0{\cdot}1°$. If the bath was heated, a pressure of about 500 atm. was first applied to prevent liquid from expanding out of the glass tube.

FIG. 1.



The rate of increase of pressure was controlled to allow time for the heat of compression to dissipate. Pressure was increased between contact points by about 500 atm. every 10 minutes. When the new contact was made, pressure was released until the contact was just broken, and ½ hour was allowed for the temperature to become steady. The contact was then remade by creating extra pressure in the pump and opening the valve to the intensifier very slowly. Two, and often three, runs were carried out to establish each isotherm.

Calculation of Results and the Experimental Error.—The compression or fractional decrease in volume $h = \Delta V/V_0$, where V_0 is the initial volume, was calculated from the density of the liquid and from the known volume of the tube at each contact as determined by the calibration. The tube volumes were corrected for temperature change by using the following coefficients of cubic expansion: Jena glass $0{\cdot}2533 \times 10^{-4}$; Pyrex $0{\cdot}108 \times 10^{-4}$. The correction for the compression of the glass of the tube was made by subtracting the compression of the glass from the calculated compression of the liquid. The appropriate values are: $k_{Jena} \times 10^6 = 2{\cdot}206 + 0{\cdot}0028t$ per atm.; $k_{Pyrex} \times 10^6 = 3{\cdot}00$ per atm., as determined by Perman and Urry (*Proc. Roy. Soc.*, 1928, **40**, 186) and Adams and Gibson (*J. Washington Acad. Sci.*, 1931, **21**, 381).

Repeated recalibrations were performed, and in one test a calibrated tube was placed under 5000 atm. pressure for 5 hours. In no case were the variations found sufficient to affect the final volumes recorded in Table II by more than 0·02%. The possible error in the weighings could produce a variation of $\pm 0{\cdot}01\%$ in the final volumes.

The Bourdon gauge, on the low-pressure side of the intensifier, was calibrated against a pressure balance accurate to 1 atm., and could be read to ± 1 atm. The intensifier ratio (approx. 5 : 1) is not as large as that calculated from the ratio of the cross-sectional areas of the two pistons comprising the intensifier, and it was found to vary with the pressure used, presumably because of the changing areas of contact between the pistons and the cylinder walls. The ratio was determined over the whole pressure range and found to alter appreciably at the lower pressures but to become constant above 300 atm. (low-pressure side).

From these considerations it appears that the maximum accuracy is attained at pressures above 1000 atm. and that the volumes determined in this range are accurate to within about $\pm 0{\cdot}04\%$.

Materials.—*n*-Heptane and *n*-octane were synthetic products obtained from the Eastman-Kodak Co.; *n*-hexane was supplied by the Anglo-Iranian Oil Co. The hydrocarbons were shaken with concentrated sulphuric acid, washed with distilled water, and refluxed over calcium turnings. They were then fractionated, a middle fraction boiling over a temperature range not exceeding 0·15° being collected. Samples were de-ærated in an all-glass apparatus before use. The boiling ranges and refractive indices were as follows: *n*-hexane 68·8—68·85°, n_D^{20} 1·3750; *n*-heptane 98·4—98·5°, n_D^{25} 1·3844; *n*-octane 125·4—125·55°, n_D^{20} 1·3975.

For the calculations, it was necessary to know the densities of the liquids and mixtures at the temperatures employed. There was not sufficient material to allow determination of density–composition curves at all four temperatures, so the following procedure was used. The densities of the pure liquids at 25° and 40° were accurately determined in a specific gravity bottle and found to be in excellent agreement with those given in International Critical Tables. The densities of two mixtures of each of the three pairs of liquids were also determined at these two temperatures and it was found that the liquids mixed without change in volume. It was therefore considered justifiable to use the density–temperature equation given in I.C.T. to calculate the densities of the liquids at the other two temperatures, and to compute the densities of the mixtures additively. In Table I are given the constants of the specific volume–temperature equation for the pure hydrocarbons expressed in the form:

$$V = V_0 + \alpha t + \beta t^2 + \gamma t^3$$

where V_0 s the specific volume at 0°.

The composition of the mixtures at 25° was checked against a refractive index–composition curve for the sodium *D* line, determined with an Abbé refractometer. A straight-line relationship

was found, the heptane–octane mixtures, for example, being represented by the equation $n_D^{20} = 1{\cdot}072 \times 10^{-4}w + 1{\cdot}3844$, where w is the weight % of *n*-octane in the mixture. In no case was there a significant change in the composition of a mixture during the experiments.

TABLE I.

Thermal expansion coefficients.

	V_0.	$\alpha \times 10^3$.	$\beta \times 10^6$.	$\gamma \times 10^3$.
n-Hexane	1·4770	1·851	4·714	0·9524
n-Heptane	1·4275	1·717	2·102	1·024
n-Octane	1·3918	1·599	0·817	1·309

TABLE II.

Relative volumes.

Press. (atm.)	Volume 0°	25°	40°	60°	Press. (atm.)	Volume 0°	25°	40°	60°
				n-Hexane.					
1	1·0000	1·0334	1·0556	1·0881	3000	0·8446	0·8561	0·8636	0·8741
500	0·9501	0·9729	0·9876	1·0085	3500	0·8327	0·8434	0·8503	0·8600
1000	0·9175	0·9357	0·9475	0·9642	4000	0·8221	0·8319	0·8386	0·8477
1500	0·8934	0·9089	0·9190	0·9333	4500	0·8126	0·8219	0·8280	0·8369
2000	0·8742	0·8880	0·8969	0·9095	5000	0·8040	0·8128	0·8186	0·8268
2500	0·8582	0·8707	0·8788	0·8903					
		n-Heptane.					*n*-Octane.		
1	1·0000	1·0311	1·0509	1·0790	1	1·0000	1·0289	1·0475	1·0731
500	0·9538	0·9760	0·9896	1·0085	500	0·9596	0·9807	0·9942	1·0119
1000	0·9229	0·9409	0·9520	0·9672	1000	0·9313	0·9487	0·9596	0·9739
1500	0·8996	0·9153	0·9249	0·9379	1500	0·9096	0·9247	0·9342	0·9465
2000	0·8811	0·8949	0·9035	0·9151	2000	0·8919	0·9053	0·9138	0·9248
2500	0·8654	0·8782	0·8860	0·8965	2500	0·8771	0·8993	0·8971	0·9069
3000	0·8521	0·8639	0·8711	0·8809	3000	0·8642 •	0·8755	0·8827	0·8919
3500	0·8404	0·8514	0·8582	0·8673	3500	—	0·8635	0·8702	0·8788
4000	0·8301	0·8403	0·8467	0·8553	4000	—	0·8528	0·8591	0·8672
4500	0·8206	0·8304	0·8364	0·8445	4500	—	0·8431	0·8489	0·8567
5000	0·8121	0·8214	0·8272	0·8348	5000	—	0·8342	0·8399	0·8472

• Freezes above this pressure.

TABLE III.

Constants of Tait's equation.

For all liquids and mixtures at all temperatures, $C = 0{\cdot}2172$.

Liquid	B (atm.) 0°	25°	40°	60°
n-Hexane	713·9	579·1	508·6	424·5
n-Heptane	788·6	653·1	582·9	498·8
n-Octane	931·4	776·5	696·8	599·1
C_7–C_8 Mixtures:				
22·04% C_8	816·4	678·2	605·2	518·8
41·32% „	841·8	700·7	625·1	537·4
65·37% „	876·1	731·6	653·7	561·8
82·73% „	902·4	752·8	674·5	581·0
C_7–C_9 Mixtures:				
31·93% C_7	736·9	602·0	531·5	446·8
65·73% „	762·2	626·8	556·3	471·7
C_8–C_9 Mixtures:				
33·82% C_8	778·7	638·2	564·7	476·1
61·48% „	837·9	692·6	615·8	523·9
Ternary mixtures:				
35·26% C_8; 31·72% C_7; 33·02% C_9	803·1	662·5	588·5	500·1
19·11% C_8; 41·16% C_7; 40·73% C_9	810·4	670·9	597·4	509·5

(All compositions are given as weight percentages.)

Results.—The experimental points were plotted and, from the smooth pressure–volume isotherms drawn through them, volumes were read off at intervals of 500 atm. pressure. These values for the pure liquids are shown in Table II. The results for the pure hydrocarbon at 0° correspond well with those of Bridgman (*Proc. Amer. Acad. Arts Sci.*, 1931, **66**, 185), who uses kg./cm.² as his pressure unit.

All the P–V–T data may be expressed accurately by the Tait equation (see p. 3089), *viz.*,

$$\Delta V/V_0 = k = C \log (B + P)/(B + P_0)$$

where B and C are constants and k is the compression, or fractional change in volume, when the pressure

changes from P_0 to P. Table III gives the values of B for the pure liquids and their mixtures at the four temperatures. The constant $C = 0{\cdot}2172$ and is found to be the same for all the liquids and their mixtures and to be independent of temperature. (*N.B.* Gibson's usage has been followed in giving the value of C. If the Tait equation is expressed in terms of natural logarithms, $0{\cdot}4343C$ must replace the above figure).

Discussion.

1. *Tait's Equation.*—This equation was found by Tait (1888) to fit the compression data for water. Wohl (*Z. physikal. Chem.*, 1921, **99**, 234) and Carl (*ibid.*, 1922, **101**, 238) found that it satisfactorily represented Amagat's (*loc. cit.*) and Bridgman's data (*Proc. Amer. Acad.*, 1913, **49**, 1), and noted the temperature-independence of C. Gibson and his associates (*loc. cit.*; see also *J. Amer. Chem. Soc.*, 1934, **56**, 4; 1935, **57**, 284) have made a thorough study of the equation and find that it closely fits Adams's data (*ibid.*, 1931, **53**, 3769) on water up to 10,000 bars at 25°, and Bridgman's results (*Proc. Amer. Acad. Arts Sci.*, 1931, **66**, 185; 1932, **67**, 1; 1933, **68**, 1) on numerous non-volatile liquids at different temperatures over the same range. Gibson finds that C has the same value ($= 0{\cdot}21591$) for benzene, chlorobenzene, bromobenzene, aniline, and nitrobenzene; and for aniline–nitrobenzene, aniline–benzene, and aniline–chlorobenzene mixtures—an example which parallels the constancy of C for the hydrocarbons and hydrocarbon mixtures described in this paper.

The theoretical basis of Tait's equation is still very obscure. The temperature-independence of C, and the fact that it varies little from liquid to liquid, have led to the supposition that it depends on the repulsive forces between the molecules.

Gibson and Kincaid (1938, *loc. cit.*) have tentatively identified $B + P$ with the difference between the expansive thermal or kinetic contribution to the pressure and the internal attractive pressure. They write $P = T.f(V) + \phi(V) + \psi(T)$, in which $T.f(V)$ is the kinetic contribution to the pressure, $\phi(V)$ is the purely volume-dependent part of the internal pressure, arising from the attractive forces, and $\psi(T)$ is the temperature-dependent difference between the attractive pressure and the kinetic repulsion which is regarded as equal to B. $\psi(T)$ is generally a cohesion in liquids and is balanced by the intermolecular repulsions. B decreases with increasing temperature and on this interpretation must change sign at the critical temperature.

For the liquids that Gibson investigated $(\partial P/\partial T)_V$ was found to be not a pure function of volume but to vary slightly with temperature. This appears to indicate interaction between the component terms of P in the above equation. It is thus doubtful whether precise physical significance can be attached to these terms, and hence to B or $B + P$, for liquids in which $(\partial P/\partial T)_V$ is not a pure volume function. In our experimental range, as discussed below, this coefficient is temperature-invariant and Gibson's view may hold more exactly.

The ability of Tait's equation to represent the P–V isothermals adequately has been demonstrated by Gibson through a comparison of values of the compressibility, $(\partial V/\partial P)_T/V$, at 1 atm., obtained experimentally, with those calculated from Tait's equations for his liquids. The agreement was always to within 1%. Such a comparison is possible for heptane and octane, by using the adiabatic compressibilities measured by Freyer, Hubbard, and Andrews (*J. Amer. Chem. Soc.*, 1929, **51**, 759). The relation given in their paper was used to calculate the isothermal compressibilities, values for the specific heats being taken from Parks, Huffman, and Thomas (*ibid.*, 1930, **52**, 1033). The satisfactory agreement found is shown in Table IV.

Table IV.

Isothermal compressibilities at 1 *atmosphere* ($\times 10^6$).

Liquid	0°	25°	40°	60°	Source
n-Heptane	119·5	144·2	161·5	188·7	Tait's equation
,,	121·4	146·0	163·7	190·1	F, H, and A
n-Octane	101·2	121·3	135·2	157·2	Tait's equation
,,	103·7	123·2	138·4	159·3	F, H, and A

At the same time it was found that values of the dilatation $(\partial V/\partial T)_{P=0}$ calculated from the compressibility and the pressure coefficient by the reaction

$$\left(\frac{\partial V}{\partial T}\right)_{P=0} = \left(\frac{\partial V}{\partial P}\right)_T \times \left(\frac{\partial P}{\partial T}\right)_V,$$

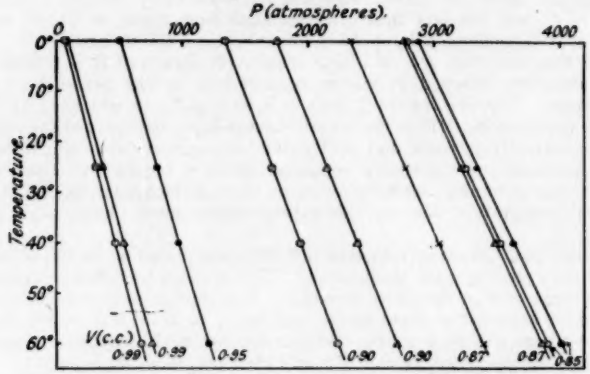
agreed satisfactorily with those obtained from specific-volume measurements for all three hydrocarbons.

2. *The Pressure Coefficient* $(\partial P/\partial T)_V$.—For all the liquids and their mixtures, the isochores are straight lines, within the experimental error, as shown by the examples in Fig. 2. The pressure coefficients, $(\partial P/\partial T)_V$, are thus pure volume functions within the range investigated. The coefficients decrease with increasing volume at constant temperature.

There is a conflict of evidence as to whether or not the pressure coefficient for liquids is in general a pure volume function. Gibson found a small but definite degree of temperature-dependence at constant volume for all the liquids that he measured. Among these were ethylene glycol and highly polar monosubstituted benzenes, but they also included benzene itself and carbon tetrachloride. Bridgman (1913, *loc. cit.*) also finds a temperature variation in a series of polar liquids and presents detailed calculations for the case of carbon disulphide. Hildebrand (*Physical Rev.*, 1929, **34**, 984) attributes the variations found by Bridgman to experimental irregularites, at least in the case of ether (the most symmetric and least polar liquid studied), and gives an interesting discussion of intermolecular forces in this substance. Subsequently, Bridgman (1931, *loc. cit.*) presented new data which also indicate a variation of the pressure coefficient at constant volume, and advanced general reasons (*Rev. Mod. Physics*,

FIG. 2.

Liquid isochores.



○ *n*-Hexane. × *n*-Heptane. △ *n*-Octane. ● 31·93% Heptane.

1935, **7**, 1), based on molecular deformability, for supposing that this is normally to be expected. These data include results for normal hydrocarbons up to 10,000 kg./cm.², but only three isotherms (at 0°, 50°, and 95°) were determined, and a small error in one of these would invalidate his conclusions. A variation would perhaps be more apparent over Bridgman's greater pressure range, but within the limits of the present measurements the coefficients for *n*-hexane, *n*-heptane, and *n*-octane are sensibly constant at constant volume. From all the available data it appears likely that liquids whose molecules have permanent dipoles do show a change with temperature in the pressure coefficient, but that for some, though certainly not all, non-polar liquids, having symmetrical molecules, the variation of the coefficient at constant volume is either non-existent or negligibly small.

3. *The Energy–Volume Coefficient,* $(\partial E/\partial V)_T$.—This coefficient is the left-hand member of the so-called " thermodynamic equation of state : "

$$(\partial E/\partial V)_T = T(\partial P/\partial T)_V - P$$

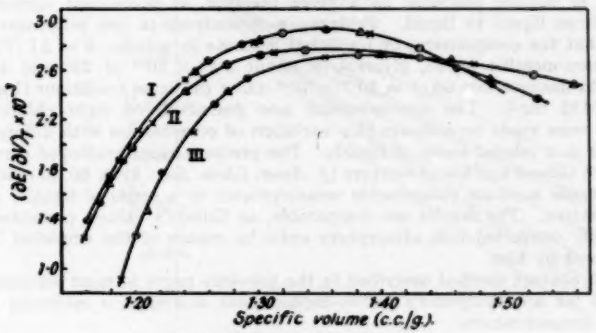
(E being the internal energy). When the pressure coefficient is a function of volume alone, $(\partial E/\partial V)_T$ is also necessarily a pure volume function. That this is so for the three normal hydrocarbons and their mixtures is shown in Fig. 3, where three typical curves are given for two pure liquids and one binary mixture. The points for the different temperatures all fall on one curve. Similar curves given by Gibson for his liquids show a displacement with temperature amounting to about 10% of the value of the energy–volume coefficient, for benzene and its derivatives between 25° and 65°, and about 6 or 7% for carbon tetrachloride. Water gives very much larger changes with temperature.

At a sufficiently high pressure the energy–volume coefficient passes through zero. Our pressure range does not include this point but, as Bridgman has found for other liquids, it appears to be at about 7000 atm., or somewhat higher. The preliminary decrease of $(\partial E/\partial V)_T$ through positive values up to this pressure implies that more energy flows out as heat to maintain isothermality than is put in as mechanical work, *i.e.*, the attractive forces in the liquid predominate. If the molecules are undeformable in this range, the molecular volume at the pressure at which $(\partial E/\partial V)_T = 0$ should be the same as that at 0° K. and 1 atm. Hildebrand (1929, *loc. cit.*) showed that this was so for ether, as far as can be estimated, and Bridgman (1931, *loc. cit.*) obtains a similar approximate equality for *n*-pentane. It may be expected that *n*-hexane, *n*-heptane, and *n*-octane would behave in the same way.

4. *The Attractive Internal Pressure.*—The equation of state $(\partial E/\partial V)_T = T\gamma - P$, in which, following Hildebrand, γ denotes $(\partial P/\partial T)_T$, has been combined by Gibson with Tait's equation constant B. The coefficient $(\partial E/\partial V)_T$ is regarded as being the sum of attractive and repulsive components $(\partial E_R/\partial V)_T + (\partial E_A/\partial V)_T$ and Gibson's identification of $B + P$ with the repulsive internal pressure leads to an expression for the attractive internal pressure $(\partial E_A/\partial V)_T = T\gamma + B$.

FIG. 3.

Energy–volume coefficients.



I, n-*Octane*.
II, 22·04% *Octane*–77·96% *heptane*.
III, n-*Hexane*.

× 0°. ⊙ 25°. △ 40°. ● 60°.

This quantity is a pure volume function for most of the liquids investigated by Gibson and is expressible in the form a'/V^x, the exponent of V averaging 2·74 for benzene derivatives. We also obtain straight lines, including points at each temperature, for plots of log $(T\gamma + B)$ against log V. The slopes give an average value of $x = 3{\cdot}5$ for the pure liquids and their mixtures, and $a' \times 10^{-8}$ is repectively 0·4524, 1·494, and 1·191 for hexane, heptane, and octane. As Gibson has pointed out, it is unlikely that this relation holds down to the lowest pressures.

5. *The Volume Change on Mixing.*—The three normal paraffins investigated mix without expansion or contraction at all pressures and temperatures. An illustration is afforded by the following results for a 34·62% heptane–65·38% octane mixture at 25° :

Relative volumes.

Pressure (atm.)	1	1000	2000	3000	4000	5000
V (additive)	1·0295	0·9459	0·9016	0·8716	0·8480	0·8296
V (observed)	1·0296	0·9464	0·9016	0·8714	0·8484	0·8297

This behaviour may be contrasted with the divergencies found by Gibson and Loeffler (*J. Amer. Chem. Soc.*, 1939, **61**, 2877) for aniline–nitrobenzene mixtures.

DEPARTMENT OF CHEMICAL ENGINEERING,
IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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684. *Pressure–Volume–Temperature Relations in Liquids and Liquid Mixtures. Part II.* The Compression Isotherms of Some Organic Liquids up to 1000 Atmospheres, and the Compressions of Some Aqueous and Non-aqueous Binary Liquid Mixtures.*

By D. M. Newitt and K. E. Weale.

The compression or fractional decrease in volume of eight chlorine-substituted hydrocarbons, and of acetone, has been measured at 25° and at pressures up to 1000 atmospheres. The relation of this quantity to other properties of the liquids is discussed.

The compression of a number of binary liquid mixtures at 25° and 1000 atmospheres has been measured over the whole composition range. Systems having water as one component show a compression minimum, which is related to other properties of these mixtures.

The decrease in volume produced by a given pressure, at a constant temperature, varies considerably from liquid to liquid. Bridgman's measurements (see references in preceding paper) show that the compression, or fractional decrease in volume, $k = \Delta V/V_0$, of the least compressible non-metallic liquid, glycerol, is about $2{\cdot}15 \times 10^{-2}$ at 25° and 1000 kg./cm.², while for a light fluorocarbon oil, $k = 10{\cdot}7 \times 10^{-2}$ under the same conditions (1 atm. = 1·0332 kg./cm.² = 1·0133 bars). The measurements now described, on eight chlorine-substituted hydrocarbons, were made to compare this variation of compression with differences in molecular structure in a related series of liquids. The pressure range employed corresponds with that over which Gibson and his co-workers (*J. Amer. Chem. Soc.*, 1938, **60**, 511, and subsequent papers) have made accurate compression measurements on a series of liquids, which include benzene derivatives. The results are comparable, as Gibson's values, presented in terms of bars, are readily converted into atmosphere units by means of the empirical Tait equation constants derived by him.

The electric contact method described in the previous paper is most accurate in a higher pressure range (as are Bridgman's piston-displacement and syphon methods) and was not used for these measurements.

Experimental.

The method used was that described by Adams (*J. Amer. Chem. Soc.*, 1931, **53**, 3769) and employed with slight modifications by Gibson (*loc. cit.*). The piezometer is of Pyrex glass and has the form shown in Fig. 1. The glass tube is closed at the top by a ground stopper having a mercury seal. From the base, a re-entrant capillary stem rises centrally inside the piezometer and is curled over at the end. The liquid to be compressed fills the piezometer, and, when pressure is applied, mercury is forced up the capillary, falls to the bottom, and remains trapped when the pressure is subsequently released. The external diameter of the piezometer is 1 cm., its overall length about 18 cm., and its internal capacity about 4 c.c. The capillary stem is about 5 cm. long and of 0·5 mm. internal diameter.

Before use the piezometer was carefully annealed (a procedure found essential by Adams and Gibson for reproducible results). Heating at 550° for 15 minutes was followed by cooling at the rate of 1°/min. for 20 minutes, and then as rapidly as the furnace would cool. The internal volume of the piezometer and of the capillary tube at 25° was determined by using mercury as filling liquid. The values accepted were the mean of several in close accordance.

The general lay-out of the high-pressure apparatus has already been described (*J.*, 1938, 784, Fig. 1). In this case, the thick-walled steel vessel (¼" inside diameter) is closed by a hard rubber "Poulter" packing held in place by a steel screw-plug. It is immersed in a thermostat bath stirred by a pump, and controlled to ±0·1°. Pressure is conveyed from a hydraulic pump to an intensifier system and thence by a steel pipe-line to the bottom of the vessel. The pressure is shown by a Bourdon gauge on the low-pressure side of the intensifier, the effective ratio of which is about 9 : 1. It is not necessary in this case to know the exact value of this ratio because on the high-pressure side of the intensifier is connected a dead-weight pressure balance which measures directly the pressure in the vessel. The pressure balance is correct to at least ±1 atm. at 1000 atm. The whole apparatus is filled with liquid paraffin, which is the pressure-transmitting medium.

Before a run, the piezometer was filled with the liquid under examination at a temperature below 25°, so that subsequent thermal expansion ensured that the tube was completely filled with liquid. Care was necessary to exclude very small bubbles, and it was found that silicone stop-cock grease was

* Part I, preceding paper.

a better lubricant than " Vaseline " for the stopper, as it was less readily attacked by the liquid during insertion. The filled piezometer was placed on a quantity of clean distilled mercury in a cylindrical steel holder, which was then immersed in liquid paraffin in the pressure vessel at thermostat temperature.

The hard rubber packing was pushed in very slowly by means of a brass screw-plunger. During this operation, the return valve to the pump was open so that no pressure could be generated in the vessel. Finally, the steel plug was screwed into position.

Pressure was applied to the vessel at 5-minute intervals in 100-atm. increments. This rate of increase proved slow enough to allow the heat of compression to be dissipated. The pressure was brought to within about 20 atm. of that desired in this way, and maintained at a steady value for 5—10 minutes to ensure temperature equalisation. The final adjustment of pressure was then made by slowly turning a screw-ram incorporated in the hydraulic pump.

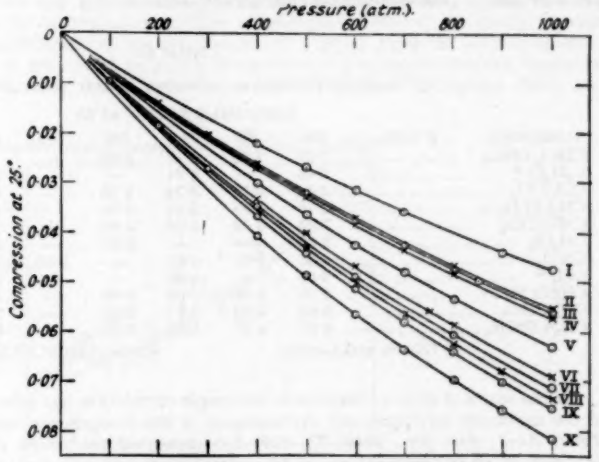
The release of pressure was also carried out at a slow uniform rate (occupying about 3 hours for a maximum pressure of 1000 atm.). The sequence of closing and opening valves by which the release

FIG. 1.

Pyrex-glass piezometer in steel container.

FIG. 2.

Compression–pressure isotherms.



I, $CHCl_2{\cdot}CHCl_2$.
II, C_6H_5Cl.
III, $CCl_3{\cdot}CCl_3$.
IV, $CH_2Cl{\cdot}CH_2Cl$.
V, $CHCl{:}CCl_2$.
VI, $CHCl_3$ *and* CH_2Cl_2.
VII, CCl_4.
VIII, $CHCl{:}CHCl$.
IX, $CH_3{\cdot}CHCl_2$.
X, $CH_3{\cdot}CO{\cdot}CH_3$.

was begun was so ordered that there was no possibility of an accidental increase of pressure, overshooting the desired maximum.

The mercury trapped in the piezometer was washed with alcohol and anhydrous ether, and weighed. The compression of the liquid is then given by

$$k = \frac{(V_{Hg})_0(1 - k_{Hg}) + (V_c)_0(1 - k_{Pyrex})}{V_0} + k_{Pyrex}$$

where k_{Hg} and k_{Pyrex} are the compressions of mercury and of the piezometer glass at 25° and the appropriate pressure; and V_0, $(V_{Hg})_0$, and $(V_c)_0$ denote respectively the volume of liquid (total inside volume of tube and capillary), the volume of mercury trapped, and the inside volume of the capillary stem at 1 atm. and 25°. Values for k_{Pyrex} and k_{Hg} were taken from the results of Adams and Gibson (*J. Washington Acad. Sci.*, 1931, **21**, 381) and Bridgman (*Proc. Amer. Acad. Arts Sci.*, 1912, **47**, 432).

All the compressions at 1000 atm. for the pure liquids are the mean of several determinations which usually agreed to within 0·5%. Many of the other compressions were also measured more than once. Occasional check runs on redistilled water gave values about a mean $k = 3{\cdot}96 \times 10^{-2}$ at 1000 atm. and 25°, which is satisfactorily close to the value $3{\cdot}98 \times 10^{-2}$ derived from Gibson and Loeffler's work (*J. Amer. Chem. Soc.*, 1941, **63**, 898). The accuracy of the measurements at 1000 atm. is thus estimated to be better than $\pm 1\%$.

The compressions of the mixtures were determined with the same accuracy, although usually only one measurement was made at any particular composition.

Materials.—Acetone (two separate samples) and chloroform were obtained in " AnalaR " quality and were used after being once fractionated in an all-glass Widmer column. The boiling ranges were 56·0—56·3° and 61·0—61·3° and the refractive indices (n_D^{20}) 1·3590 and 1·4465, respectively. The other liquids were dried ($CaCl_2$) (in some cases a preliminary shaking with dilute potassium hydroxide solution being necessary), and fractionated twice, as above. Boiling ranges were: methylene dichloride 40·0—40·2°; *trans*-dichloroethylene 48·0—48·5°: ethylidene chloride 57·3°; 1 : 2-dichloroethane 83·5—83·7°; trichloroethylene 87·0—87·5°; tetrachloroethylene 121·0—122·0°, and tetrachloroethane 146·0—146·5°. Refractive indices (n_D^{20}) were measured with an Abbé refractometer and agreed to within 0·0005 with values given in the International Critical Tables.

Discussion.

A. *Compression Isotherms of Single Liquids.*—The compressions of the eight chlorine-substituted hydrocarbons, and of acetone, are given in Table I. The values for carbon tetrachloride and chlorobenzene which are also included have been obtained from the results of Gibson and Loeffler (*loc. cit.*; *J. Amer. Chem. Soc.*, 1939, **61**, 2515) by conversion to atmosphere pressure units. The compression curves are shown in Fig. 2.

Table I.

Percentage decrease in volume of liquids under pressure.

Compression $k \times 10^6$ at 25°.

Compounds p (atm.) =	400	500	600	700	750	800	850	900	1000
$CHCl_2 \cdot CHCl_2$	2·20	2·68	3·15	3·60	—	—	—	4·41	4·78
C_6H_5Cl *	2·63	—	3·71	—	—	4·69	—	—	5·56
$CCl_2 \cdot CCl_2$	2·64	3·19	3·74	4·26	—	4·73	4·97	—	5·63
$CH_2Cl \cdot CH_2Cl$	2·70	3·28	3·84	4·34	—	4·84	—	—	5·76
$CHCl{:}CCl_2$	3·02	3·64	4·25	4·80	—	5·36	—	—	6·32
CH_2Cl_2	3·30	4·01	—	5·27	—	5·88	—	—	6·93
$CHCl_3$	3·35	4·01	4·69	—	5·59	5·89	—	—	6·93
CCl_4 *	3·53	—	4·90	—	—	6·09	—	—	7·15
$CHCl{:}CHCl$ †	3·58	4·30	5·02	5·66	—	6·26	—	6·80	7·38
$CH_3 \cdot CHCl_2$	3·69	4·43	5·15	5·82	—	6·41	—	7·03	7·56
$CH_3 \cdot CO \cdot CH_3$	4·07	4·87	5·66	6·38	—	6·96	—	7·59	8·18

* Gibson and Loeffler. † *trans*-$CHCl{:}CHCl$, b. p. 48·4°.

In the series of chloro-compounds, no simple correlation has been found between any aspect of the molecular structure and the sequence of the compression isotherms. Bridgman (*Proc. Amer. Acad. Arts Sci.*, 1949, **77**, 129) has measured the rough compressions up to 40,000 kg./cm.², at room temperature, of 30 hydrocarbons and also finds no correlation between the compressions and structural factors, such as the C : H ratio in the molecule, the type of the carbon–carbon bonds, and the type (whether straight-chain, single ring, or double ring) of the molecule. The reason is presumably that the shape and intensity of the molecular force field in the liquid is related in a complex way to the molecular structure. In the liquids of Table I, three kinds of intermolecular force are probably operative, *viz.*, the cohesive van der Waals forces opposing the thermal movement of the molecules, shorter-range intermolecular repulsions, and, in most cases, long-range dipole–dipole interaction. A change in molecular structure may, in general, be expected to affect these components in divergent ways.

The benzene derivative and the two liquids containing four chlorine atoms in the molecule are likely to be the most polarisable, and so to have the strongest cohesive forces, and these three are the least compressible of the liquids. Similarly, Bridgman (*ibid.*, 1933, **68**, 1) has shown that the compressions of alkyl halides, when the alkyl group is unchanged, decrease in the order Cl > Br > I.

Compression and Surface Tension.—A relation has been sought between the compression and some property of the liquids at normal pressure. There are indications of an approximate interdependence between the compression at a given pressure and the free energy of vaporisation. Unfortunately, there are too few experimental values of this quantity, at 25°, for an adequate comparison. There exists, however, an approximate relation between compression and surface tension which is shown in Fig. 3. In this figure, the reciprocal of the compression at 1000 atm. and 25° is plotted against the surface tension at the same temperature. The numbers of the points 1—11 refer to the liquids in Table I, reading downwards. The rest are shown in Table II and refer to liquids for which k at 1000 atm. and 25° is known with comparable or better accuracy. Water and ethylene glycol cannot conveniently be shown on

TABLE II.

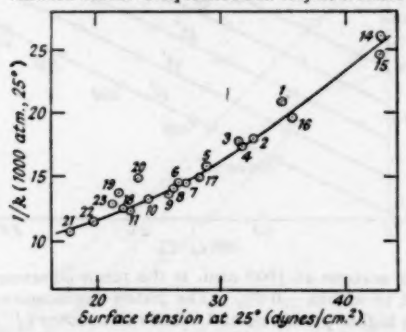
Percentage decrease in volume at 1000 atm.

Liquid	$k \times 10^3$ at 25° and 1000 atm.	Reference	Liquid	$k \times 10^3$ at 25° and 1000 atm.	Reference
12. Ethylene glycol	3·16	Gibson and Loeffler (*loc. cit.*)	18. Methanol	8·09	Gibson (see below)
13. Water	3·98		19. Ethanol	7·30	This paper
14. Aniline	3·83		20. Propanol	6·75	This paper
15. Nitrobenzene	4·06		21. Hexane	9·45	Part I (preceding paper)
16. Bromobenzene	5·09		22. Heptane	8·74	
17. Benzene	6·70		23. Octane	7·79	

Fig. 3, and are in any case probably affected by hydrogen-bonding. It appears justifiable to use arbitrarily the compressions at 1000 atm., as the isotherms are all of the same form and probably do not cross before the freezing pressures are reached. The general conclusion from Fig. 3 is that the greater the net intermolecular attractive forces at ordinary pressure, the smaller is the compression at high pressures. The relationship shown is obviously inexact but is sufficient for a rough estimate of the compression of a liquid from the surface tension. At much higher pressures it may tend to break down because the intermolecular repulsive forces become far larger than they are in liquids at ordinary pressure. Bridgman (1949, *loc.*

FIG. 3.

Relation between compression and surface tension.



cit.) has shown, however, that the initial sequence of the hydrocarbon isotherms persists up to 40,000 kg./cm.², even though the volume decrements in the 20,000—40,000 interval are irregular.

Tait's Equation and Hudleston's Relation.—The isotherms of Fig. 1 may be represented by Tait's equation

$$k = C \log (B + P)/(B + P_0)$$

where B and C are constants and P_0 is atmospheric pressure (see discussion in Part I). The values of B and C at 25° obtained from the data are shown in Table III. The data for the

TABLE III.

Constants of Tait's equation.

Liquid	C	B, atm.	Liquid	C	B, atm.
$CHCl_2 \cdot CHCl_2$	0·2156	1498	$CHCl_3$ and CH_2Cl_2	0·2391	1052
C_6H_5Cl	0·2103	1191	CCl_4	0·2126	853·9
$CCl_2 \cdot CCl_2$	0·2215	1255	$CHCl \cdot CHCl$	0·2518	1036
$CH_2Cl \cdot CH_2Cl$	0·2233	1231	$CH_3 \cdot CHCl_2$	0·2296	879·3
$CHCl \cdot CCl_2$	0·2425	1213	$CH_3 \cdot CO \cdot CH_3$	0·2356	815·0

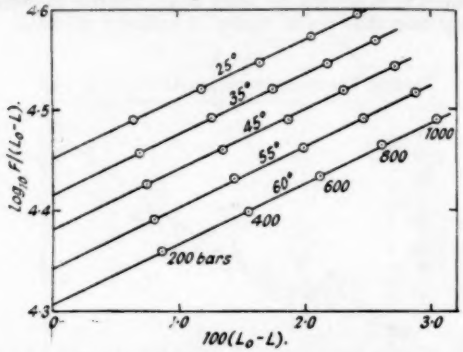
liquids also fit the straight-line plot required by a relation derived by Hudleston (*Trans. Faraday Soc.*, 1937, **33**, 97) from consideration of a simple exponential law of intermolecular force. According to this, the function, $\log F/(L_0 - L)$, should vary linearly with $L_0 - L$, where L_0 and L are the length of side of a cube containing a given mass of liquid at unit pressure

and at pressure P, respectively, and where $F = L^2P$. This rule is apparently of very wide validity and holds over a large pressure range. Fig. 4 shows the lines for carbon tetrachloride (Gibson's data) at different temperatures. Bridgman's combined data on *n*-propyl alcohol at 50° up to 50,000 kg./cm.² (*Proc. Amer. Acad. Arts Sci.*, 1913, **49**, 3; *J. Chem. Physics*, 1945, **9**, 794) give a straight line over most of the range; a divergence above 35,000 atm. could be entirely attributed to a 2% error in the volume decrements. When the slopes of the lines for different liquids (each for a mass of 1 g.-mol.) are compared they are found to vary by only a few units %, and for benzene and carbon tetrachloride (Gibson) the slopes are independent of temperature.

Hudleston stated that water and acetone are exceptions, but the apparent discrepancy seems due to small experimental irregularities in Bridgman's data at the lower end of his pressure range. Adams's results (*loc. cit.*) for water at 25° up to 12,000 bars give a good straight line, and the data for acetone in Table I (obtained for the purpose of this comparison) give a straight line in the region below 2000 atm. in which Bridgman's results (*loc. cit.*, 1913) are

FIG. 4.

Compression data for CCl_4 *(Gibson and Loeffler) plotted according to Hudleston's equation.*
(The points are calculated for unit volume at each temperature.)



divergent. The value for acetone at 1000 atm. is the mean of seven determinations on two samples, which all agreed to within ±0·6%. The piston-displacement method only develops its maximum accuracy at higher pressures, and Gibson has shown (*J. Amer. Chem. Soc.*, 1935,

TABLE IV.

Compression of mixtures at 1000 *atm.*

(W and n refer to the first-named component in the mixture.)

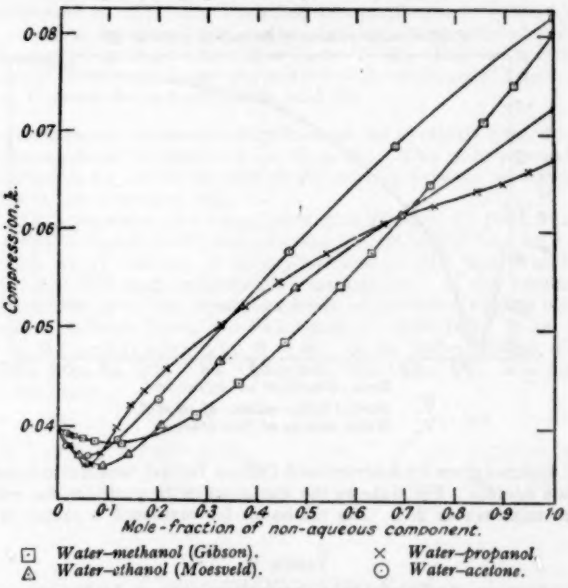
W, wt. %	n	$100k$	W, wt. %	n	$100k$	W, wt. %	n	$100k$
			Acetone–Water.					
0	0	3·96	29·71	0·1160	$3·87_5$	87·16	0·6780	6·83
5·32	0·0172	3·79	44·86	0·2016	4·27	100·00	1·0000	8·18
16·69	0·0585	3·69	73·30	0·4601	5·77			
			Propanol–Water.					
6·44	0·0202	3·80	40·65	0·1703	4·33	86·25	0·6529	6·05
15·79	0·0533	3·60	48·03	0·2186	4·57	91·24	0·7577	6·24
17·90	0·0613	3·62	61·81	0·3270	5·01	94·65	0·8411	6·42
23·55	0·0845	3·71	66·70	0·3754	5·20	96·56	0·8945	6·47
30·29	0·1153	3·98	72·46	0·4412	5·47	98·40	0·9488	6·62
35·46	0·1415	4·21	79·66	0·5404	5·76	100·00	1·0000	6·75
			Acetone–Chloroform.					
0	0	6·93	39·42	0·5724	7·65	78·73	0·8818	8·08
4·87	0·0950	7·02	53·10	0·6993	7·85	100·00	1·0000	8·18
22·55	0·3745	7·37	69·25	0·8220	8·02			
			Ethanol–Propanol.					
0	0	6·75	43·71	0·5034	7·02	100·00	1·0000	7·30
11·12	0·1405	6·79	89·91	0·9208	7·27			

57, 1551) that methanol also undergoes a greater compression at 1000 bars than Bridgman's values indicate. Hudleston's equation is thus a useful check on experimental results, but its theoretical basis remains obscure and its application is limited by the fact that it cannot be transformed into a simple expression for volume as a function of pressure.

B. *Compressions of Binary Liquid Mixtures.*—The object of these measurements, at 25° and 1000 atm., was to find whether the compressions of the mixtures can be calculated additively from those of the pure components, or whether there are major departures from the straight-line compression–composition graph which this implies. Data already available include results for the methanol–water and acetic acid–water systems at 25° and 1000 bars (Gibson, 1935, *loc. cit.*, and *ibid.*, p. 284), ethanol–water at 25° and 500, 1000, and 1500 atm. (Moesveld, *Z. physikal. Chem.*, 1923, **105**, 450), the extensive measurements on aniline–nitrobenzene, aniline–benzene, and aniline–chlorbenzene mixtures by Gibson and Loeffler (*loc. cit.*, 1939; *J. Physical Chem.*, 1939, **43**, 207), and the values for hydrocarbon mixtures in Part I

FIG. 5.

Compression of aqueous binary mixtures at 1000 *atm.*, 25°.



of this series. Dolezalek and Speidel (*Z. physikal. Chem.*, 1920, **94**, 72) have measured the compressibilities, $\beta = -(\partial V/\partial P)_T/V$, of benzene–carbon tetrachloride, benzene–ethylene dichloride, and chloroform–ether mixtures at pressures from 30 to 600 kg./cm.², but these results are not in a form in which they can be compared with the others. Richards and Chadwell (*J. Amer. Chem. Soc.*, 1925, **47**, 2283) have examined the depression in the compressibility of water produced by ether, ethanol, urethan, and methyl acetate at low concentrations, and have measured average compressibilities in the range 100—300 bars.

The results now presented are for the mixtures acetone–water, propanol–water, ethanol–propanol, and acetone–chloroform, and are given in Table IV, where n is the mole-fraction and k the compression at 25° and 1000 atm. The greatest departure from additivity so far found in non-aqueous mixtures occurs in the aniline–benzene system (Gibson and Loeffler) which has a lower compression than would be expected from the values for the pure components. The maximum divergence at 25° and 1000 bars amounts to about 5%. The compressions of aniline–nitrobenzene mixtures are up to 1% greater than additive under the same conditions. Both ethanol–propanol and acetone–chloroform (Table IV) give a linear compression–composition relation within the experimental error. Strong interaction occurs in the last-named

system, but presumably after the molecular complexes have been formed the " intermolecular " forces are similar to those in the pure liquids, as far as compression is concerned.

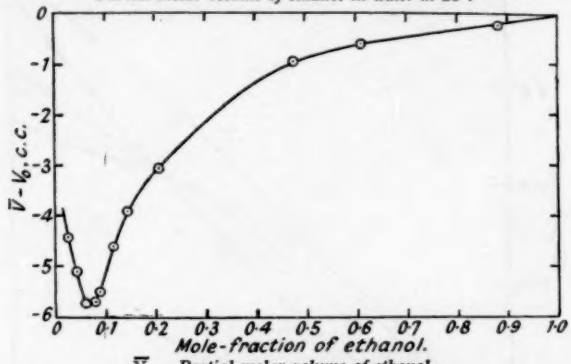
The compressions for the two aqueous mixtures, and the previous data of Gibson and of Moesveld for methanol–water and ethanol–water, are shown in Fig. 5. All the curves pass through a minimum at low concentrations of the non-aqueous component, the sharpness and position of the minimum varying from mixture to mixture. Also in the middle of the composition range the compression of the propanol–water mixtures is 3—4% above that to be expected additively.

The existence of the compression minima may be correlated with other properties of these mixtures. At similar concentrations there occur maxima in the velocity of ultrasonic waves in the mixtures (Burton, *J. Acoust. Soc. Amer.*, 1948, **20**, 186), and so presumably minima of adiabatic compressibility. Table V compares the compositions at which compression minima occur with those corresponding to the velocity maxima as estimated from Burton's curves.

Also tabulated are the maxima in the heats of mixing derived from Bose's results (*Z. physikal. Chem.*, 1907, **58**, 585), and two values for minimum partial molar volumes (calculated

FIG. 6.

Partial molar volume of ethanol in water at 25°.



$\bar{V}$. *Partial molar volume of ethanol.*
V_0. *Molar volume of pure ethanol.*

from the specific volumes given by International Critical Tables), which also appear to be related to the compression minima. Fig. 6 shows the minimum in the partial molar volume of ethanol in ethanol–water mixtures at 25°. The minimum for methanol is rather broader and less pronounced.

TABLE V.

Compositions at which maxima or minima in various properties occur.

	Mol.-fractions of non-aqueous component.			
	Methanol.	Ethanol.	Propanol.	Acetone.
Compression minimum (at 25°; 1000 bars or atm.)	0·125	0·09	0·06	0·06
Ultrasonic velocity maximum (at 25° or 27°)	0·18	0·11	0·05	0·07
Maximum heat of mixing at 25°	~0·25	~0·15	~0·08	—
Minimum partial molar volume at 25°	0·12	0·07	—	—

As would be expected from the findings for pure liquids, it seems evident that the compression minima at 1000 atm. occur in a concentration region in which the cohesive internal forces in the mixtures are strongest.

DEPARTMENT OF CHEMICAL ENGINEERING,
IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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685. *Studies in the Polyene Series. Part XXXIX.* Miscellaneous Syntheses from Ethynylcyclohexene of Acetylenic Compounds Related to Vitamin A.*

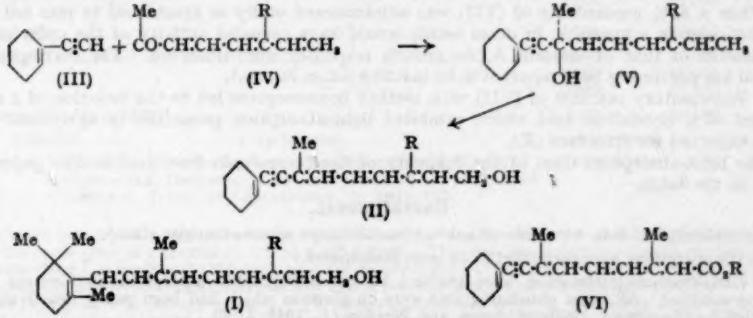
By H. Bader, B. C. L. Weedon, and R. J. Woods.

Reduction of the methyl ester of the higher-melting form of 8-*cyclo*hexenyl-2 : 6-dimethylocta-1 : 3 : 5-trien-7-yne-1-carboxylic acid (VI; R = H) with lithium aluminium hydride yielded the crystalline C_{17} alcohol (II; R = Me).

Reaction of ethynyl*cyclo*hexene (III) with octa-3 : 5 : 7-trien-2-one (IV; R = H) and with penta-2 : 4-dien-1-al gave 1-*cyclo*hexenyl-3-methylnona-4 : 6 : 8-trien-1-yn-3-ol (V; R = H) and 1-*cyclo*hexenylhepta-4 : 6-dien-1-yn-3-ol (IX), respectively. The former, on anionotropic rearrangement, was converted into the highly unstable primary C_{18} alcohol (II; R = H). Rearrangement of (IX) furnished 7-*cyclo*hexenylhepta-2 : 4-dien-6-yn-1-ol (VIII) which on treatment with acetone and aluminium *tert.*-butoxide gave 10-*cyclo*hexenyldeca-3 : 5 : 7-trien-9-yn-2-one (VII). This was condensed with methyl bromoacetate and zinc and led to 10-*cyclo*hexenyl-2-methyldeca-1 : 3 : 5 : 7-tetraen-9-yne-1-carboxylic acid (X).

The present communication records investigations on the synthesis from ethynyl*cyclo*hexene of various substances related to vitamin A (I; R = Me). This work was undertaken as part of a general programme for the elucidation of the relation between molecular structure and biological activity in the vitamin-A field.

In part XXXIV (Cheeseman, Heilbron, Jones, and Weedon, *J.*, 1949, 3120) the synthesis was described of the biologically active C_{17} alcohol (II; R = Me), bearing a close structural relation to vitamin A, by reaction of ethynyl*cyclo*hexene (III) with 6-methylocta-3 : 5 : 7-trien-2-one (IV; R = Me) and anionotropic rearrangement of the resulting alcohol (V; R = Me). The preparation of two crystalline forms of the corresponding acid (VI; R = H) was reported earlier (Heilbron, Jones, and Richardson, *J.*, 1949, 287). It has now been shown that reduction of the methyl ester (VI; R = Me) of the higher-melting acid with lithium aluminium hydride gives, in 55% yield, the crystalline alcohol (II; R = Me) identical with that previously described.



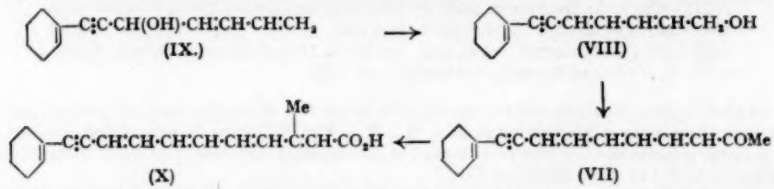
Concurrently, with the preparation of (II; R = Me) from (IV; R = Me), the synthesis of the lower homologue (II; R = H) by an analogous route was studied. Condensation of penta-2 : 4-dien-1-al (Woods and Sanders, *J. Amer. Chem. Soc.*, 1947, **69**, 2926) with acetone occurred readily in the presence of aluminium *tert.*-butoxide to give (25—40% yield) the required intermediate, octa-3 : 5 : 7-trien-2-one (IV; R = H). The structure of the latter was confirmed by its hydrogenation to hexyl methyl ketone.

When the Grignard reagent from ethynyl*cyclo*hexene (III) reacted with (IV; R = H) a product was obtained which was shown by light-absorption measurements to contain *ca.* 65%

* Part XXXVIII, *J.*, 1951, 2687.

of the tertiary alcohol (V; R = H). Anionotropic rearrangement of the latter, by treatment with 1% sulphuric acid, yielded the impure isomer (II; R = H), which was isolated as an approximately 40% concentrate by chromatography, and was characterised by formation of the *p*-phenylazobenzoate, m. p. 114°. This concentrate polymerised rapidly, even at 0° in an inert atmosphere, and consequently further purification of the primary alcohol was not attempted and no significant biological assays were possible. The difference in stability of (II; R = H) and its $C_{(3)}$-methyl homologue (II; R = Me) was very marked. Similar, though less pronounced, differences in stability have previously been observed between the methyl ether and the acetate of (I; R = H) and the corresponding derivatives of vitamin A (I; R = Me) (Cheeseman, Heilbron, Jones, Sondheimer, and Weedon, *J.*, 1949, 1516).

Oxidation of an αβ-unsaturated primary alcohol with aluminium *tert.*-butoxide and acetone to the corresponding aldehyde which, under the conditions of the reaction, condenses with excess of acetone yielding a polyene ketone, has been utilised on a number of occasions as a means of extending a polyene chain (see for example Schinz, Ruzicka, Seidel, and Tavel, *Helv. Chim. Acta*, 1947, **30**, 1810; Cheeseman, Heilbron, Jones, Sondheimer, and Weedon, *J.*, 1949, 2031). As an alternative method for the synthesis of the ketone (VII), prepared earlier from (III) and octatrienal and isolated as the semicarbazone (Heilbron, Jones, Lewis, Richardson, and



Weedon, *J.*, 1949, 742), this process has been applied to the alcohol (VIII). The latter was obtained by reaction of the Grignard complex of (III) with penta-2 : 4-dien-1-al to give (IX) in 70% yield, and subsequent anionotropic rearrangement. Treatment of (VIII) with aluminium *tert.*-butoxide and acetone gave a crude product from which the ketone (VII) was isolated by use of the Girard T reagent (Girard and Sandulesco, *Helv. Chim. Acta*, 1936, **19**, 1095) and chromatography of the ketonic fraction. The ketone was characterised by the formation of the semicarbazone and the 2 : 4-dinitrophenylhydrazone, the light-absorption properties of the former derivative being in good agreement with those reported earlier (Heilbron, Jones, Lewis, Richardson, and Weedon, *loc. cit.*).

When a 85% concentrate of (VII) was administered orally in arachis oil to rats fed on a diet deficient in vitamin A, in doses which would have revealed activity of the order of one thousandth of that of vitamin A, no growth responses were observed. The corresponding alcohol has previously been reported to be inactive (*idem, loc. cit.*).

A Reformatsky reaction of (VII) with methyl bromoacetate led to the isolation of a small amount of a crystalline acid which exhibited light-absorption properties in agreement with those expected for structure (X).

The light-absorption data of the majority of the compounds described in this paper are given in the table.

Experimental.

Light-absorption data were determined in ethanol except where otherwise stated.

All the operations were performed in an inert atmosphere.

2 : 4-Dinitrophenylhydrazones were purified by chromatographic adsorption on alumina from benzene solution. All other chromatograms were on alumina which had been partly deactivated as described by Cheeseman, Heilbron, Jones, and Weedon (*J.*, 1949, 3120).

Penta-2 : 4-dien-1-al was prepared according to Woods and Sanders (*J. Amer. Chem. Soc.*, 1947, **69**, 2926) and exhibited a light-absorption maximum at 2580 Å (ε = 29,000). The 2 : 4-dinitrophenylhydrazone had m. p. 176—177° (*idem, loc. cit.*, give m. p. 176—177°); light absorption in chloroform (main band only): 3860 Å; ε = 37,500.

8-cyclo*Hex*-1′-*enyl*-2 : 6-*dimethylocta*-1 : 3 : 5-*trien*-7-*yne*-1-*carboxylic Acids* (VI; R = H).—The method of preparation differs somewhat from that previously described (Heilbron, Jones, and Richardson, *J.*, 1949, 287).

A mixture of 8-*cyclo*hex-1′-enyl-6-methylocta-3 : 5-dien-7-yn-2-one (9·9 g.) (*idem, loc. cit.*), ethyl bromoacetate (7·6 g.), benzene (80 c.c.), activated zinc wool (3·1 g.) (*cf.* Fieser and Johnson, *J. Amer. Chem. Soc.*, 1940, **62**, 575), and a trace of iodine was heated under reflux for 45 minutes. The mixture was then cooled, decanted from a small amount of unreacted zinc, and shaken with 2N-acetic acid (*ca.*

250 c.c.). The benzene solution was washed with aqueous sodium hydrogen carbonate solution, dried, and evaporated under reduced pressure. The residual oil (11·5 g.), n_D^{25} 1·5602, was dissolved in benzene (100 c.c.), toluene-*p*-sulphonic acid (42 mg.) was added, and the mixture was heated under reflux for 5 hours. The water which separated during the first 30 minutes was removed by azeotropic distillation.

	$\lambda_{max.}$, Å	$\varepsilon_{max.}$
Ketone (IV; R = H)	2910 *	32,000
	3000	36,500
Ketone (IV; R = Me) [1]	3080	31,500
Alcohol (V; R = H)	2280	19,500
	2650	38,500
	2730	36,500
Alcohol (V; R = Me) [1]	2280	18,500
	2600	27,500
	2700	38,000
	2800	31,500
p-Phenylazobenzoate of (II; R = H) †	3230	59,000
p-Phenylazobenzoate of (II; R = Me) [2] ‡	3250	56,500
Alcohol (IX)	2270	32,000
[3]	2270	39,000
	2370	30,000
Alcohol (VIII), solid	2820 *	28,000
	2910	29,000
	3050 *	25,500
Alcohol (VIII), liquid	2820	24,500
	2910	25,500
	3040	21,500
[2]	2910	21,500
	3060	15,000
p-Phenylazobenzoate of (VIII) †	2680 *	17,000
	3080	40,500
	3290 *	19,000
Ketone (VII)	2630	9,500
	3500	35,500
[3]	2450	18,000
	3350	23,000
Acid (X)	3600	38,500
Acid (VI; R = H),[3] m. p. 179°	2570	11,000
	2600	12,000
	3390	27,500
Ester (VI; R = Me)	3450	34,000

* Inflexion. † In hexane. ‡ In chloroform.

[1] Cheeseman, Heilbron, Jones, Sondheimer, and Weedon, *J.*, 1949, 2031.
[2] Cheeseman, Heilbron, Jones, and Weedon, *J.*, 1949, 3120.
[3] Heilbron, Jones, and Richardson, *J.*, 1949, 287.

The mixture was cooled, washed with aqueous sodium hydrogen carbonate, dried, and evaporated, giving the crude ester as a viscous oil (11·5 g.), n_D^{25} 1·6200. This was dissolved in a solution of potassium hydroxide (30 g.) in methanol (300 c.c.), and the solution kept at 20° for 72 hours. Water (900 c.c.) was added, the non-hydrolysable material was extracted with ether, and the aqueous solution was then acidified (to pH 4) with phosphoric acid. The liberated acid was isolated with ether, and crystallised from the same solvent yielding acid " A " as pale yellow needles (2·1 g.), m. p. 179—180° (Heilbron, Jones, and Richardson, *loc. cit.*, give m. p. 179°). Evaporation of the ethereal mother liquors and crystallisation of the residue from aqueous methanol gave acid " B " as needles (1·68 g.), m. p. 151—152° (*idem*, *loc. cit.*, give m. p. 153°).

In another experiment, the crude dehydrated ester (6·0 g.), n_D^{25} 1·6200, was dissolved in light petroleum (b. p. 40—60°; 25 c.c.), and the solution was poured on to a column of alumina (600 g.; grade IV). The chromatogram was developed first with the same solvent and then with a mixture (1 : 2) of benzene and light petroleum (b. p. 40—60°). The least strongly adsorbed band was eluted, giving an oil (3·7 g.), n_D^{25} 1·6283. Distillation yielded *ethyl* 8-cyclo*hex*-1′-*enyl*-2 : 6-*dimethylocta*-1 : 3 : 5-*trien*-7-*yne*-1-*carboxylate* (3·35 g.) as a mixture of geometrical isomers, b. p. 120° (bath temp.)/10^{-4} mm., n_D^{25} 1·6470, which partially solidified when kept at 0° (Found : C, 80·1; H, 8·65. $C_{19}H_{24}O_2$ requires C, 80·25; H, 8·5%). Light absorption : see table.

9-cyclo*Hex*-1′-*enyl*-3 : 7-*dimethylnona*-2 : 4 : 6-*trien*-8-*yn*-1-*ol* (II; R = Me).—A solution of the acid "A" (380 mg.), m. p. 179°, in ether (25 c.c.) was cooled to 0° and treated with an ethereal solution of diazomethane (50% excess; standarised against benzoic acid). After the mixture had been kept at 0° for 5 minutes, it was warmed to 30° to expel the excess of diazomethane, and the solvent was then removed under reduced pressure giving the methyl ester as a viscous oil which solidified at 0° and exhibited a light-absorption maximum at 3400 Å; $E^{1\%}_{1\,cm.}$ = 1840.

A solution of the methyl ester in ether (10 c.c.) was added dropwise to a stirred ethereal solution of lithium aluminium hydride (1·69% wt./vol.; 4·6 c.c.) at −65°. The mixture was stirred for 75 minutes at −30°, the unreacted hydride was then decomposed by the addition of ethyl acetate (0·2 g.), and the alcohol liberated by the addition of saturated aqueous ammonium chloride (0·66 c.c.). The temperature of the mixture was allowed to rise to 20°, the mixture was then filtered and the solid washed well with ether. The combined ethereal solutions were evaporated under reduced pressure giving a yellow viscous oil, n_D^{22} 1·618. Light absorption: maxima 2560 and 3200 Å; $E^{1\%}_{1\,cm.}$ = 690 and 1280, respectively; inflexion, 3380 Å; $E^{1\%}_{1\,cm.}$ = 1000.

The crude alcohol solidified on trituration with pentane (2 c.c.). Recrystallisation from the same solvent gave the alcohol (180 mg.) as needles, m. p. 75—76° (Cheeseman, Heilbron, Jones, and Weedon, *J.*, 1949, 3120, give m. p. 75—76°). The anthraquinone-2-carboxylate, prepared from the crude alcohol, crystallised from acetone in crimson plates, m. p. 154°, undepressed on admixture with an authentic specimen (*idem*, *loc. cit.*, give m. p. 154—156°).

Similar reduction of the isomeric mixture of ethyl esters (3·0 g.) described above gave a mixture of alcohols (2·45 g.), n_D^{22} 1·6232. Light absorption: maxima, 2500 and 3200 Å; $E^{1\%}_{1\,cm.}$ = 820 and 1580, respectively. Inflexion, 2800; $E^{1\%}_{1\,cm.}$ 630. Attempts to isolate the crystalline alcohol by low-temperature crystallisation or by chromatography were unavailing. A portion (250 mg.) of the crude alcohols was converted into the anthraquinone-2-carboxylates, one of which was isolated as crimson plates (97 mg.), m. p. 154° undepressed on admixture with the derivative described above.

Treatment of the acid "B" (700 mg.), m. p. 151—152°, with diazomethane gave the crude methyl ester (700 mg.) as a pale yellow oil which exhibited a light-absorption maximum at 3480 Å; $E^{1\%}_{1\,cm.}$ = 1080. This on reduction with lithium aluminium hydride gave a pale yellow oil (620 mg.), n_D^{21} 1·6217, which had a light-absorption maximum at 3240 Å, $E^{1\%}_{1\,cm.}$ = 1150, indicating an appreciable content of the corresponding alcohol. Attempts to crystallise the latter and to prepare a crystalline derivative were unsuccessful.

Octa-3 : 5 : 7-*trien*-2-*one* (IV; R = H).—A mixture of penta-2 : 4-dien-1-al (6 g.), aluminium *tert.*-butoxide (18 g.), acetone (250 c.c.), and benzene (250 c.c.) was refluxed for 20 hours and then cooled and poured into dilute sulphuric acid (750 c.c.; 10% wt./vol.). The organic layer was washed free from acid, dried, and evaporated. Distillation of the residue gave the *ketone* (2·5—3·75 g.) as a yellow oil, b. p. 44—45°/0·05 mm., n_D^{22} 1·587, which polymerised rapidly even at 0° (Found: C, 78·4; H, 8·6. $C_8H_{10}O$ requires C, 78·65; H, 8·25%). Light absorption: see table. The *semicarbazone* (obtained in 70% yield) crystallised from aqueous methanol in pale yellow needles, m. p. 187° (decomp.) (Found: N, 23·8. $C_9H_{13}ON_3$ requires N, 23·45%). Light absorption: maxima 2990, 3130, and 3250 Å; ε = 53,500, 73,500, and 69,000, respectively.

Hexyl Methyl Ketone.—A solution of octa-3 : 5 : 7-trien-2-one (1 g.) in methanol (100 c.c.) was shaken in hydrogen in the presence of platinic oxide (10 mg.) until absorption was complete (565 c.c., at 17°/765 mm.; equivalent to 2·9 double bonds). The catalyst and solvent were removed and the residue (0·9 g.) n_D^{20} 1·4170, was converted into the 2 : 4-dinitrophenylhydrazone which crystallised from alcohol in orange prisms, m. p. 57° undepressed on admixture with an authentic specimen of the derivative of hexyl methyl ketone (Allen, *J. Amer. Chem. Soc.*, 1930, **52**, 2955, gives m. p. 58°).

1-cyclo*Hex*-1′-*enyl*-3-*methylnona*-4 : 6 : 8-*trien*-1-*yn*-3-*ol* (V; R = H).—1-Ethynyl*cyclo*hexene (7·6 g.) in ether (50 c.c.) was added during ½ hour to a solution of ethylmagnesium bromide (from 1·7 g. of magnesium) in ether (110 c.c.). The mixture was heated under reflux for 2 hours and then cooled to 5°. A solution of octa-3 : 5 : 7-trien-2-one (6·3 g.) in ether (80 c.c.) was added dropwise during 20 minutes and the mixture stirred vigorously at 25° for 1 hour. The Grignard complex was decomposed by the addition of ammonium chloride (13 g.) in water (40 c.c.), and the product isolated by means of ether giving the crude alcohol (12 g.), n_D^{25} 1·5405. Light absorption: maxima, 2300, 2650, 2730, and 2980 Å; $E^{1\%}_{1\,cm.}$ = 780, 1100, 750, and 270, respectively, indicating a *ca.* 65% content of the alcohol. Distillation of a portion (0·6 g.) of the crude product gave 1-cyclo*hex*-1′-*enyl*-3-*methylnona*-4 : 6 : 8-*trien*-1-*yn*-3-*ol* (0·2 g.) as a pale yellow oil, b. p. 80—85° (bath temp.)/10^{-5} mm., n_D^{25} 1·5788 (Found: C, 83·9; H, 9·05. $C_{14}H_{20}O$ requires C, 84·15; H, 8·85%). Light absorption: see table.

9-cyclo*Hex*-1′-*enyl*-7-*methylnona*-2 : 4 : 6-*trien*-8-*yn*-1-*ol* (II; R = H).—A solution of (V; R = H) (2 g.; crude) and a trace of quinol in ether (20 c.c.) was shaken with dilute sulphuric acid (100 c.c.; 1% wt./vol.) at 20° for 30 hours. The ethereal layer was then separated, washed free from acid, dried, and evaporated. The residual oil was extracted with light petroleum (b. p. 40—60°), and the extract concentrated under reduced pressure to a volume of 20 c.c. and then poured on to a column of partially deactivated alumina (80 g.; grade III—IV). The chromatogram was developed first with the same solvent and then with benzene. Elution of the most strongly adsorbed band with ether–methanol (10 : 1) and evaporation of the solvent under reduced pressure gave a yellow viscous oil (0·92 g.), n_D^{17} 1·5641. Light absorption: maxima, 2270, 3080, and 3150 Å; $E^{1\%}_{1\,cm.}$ = 600, 640, and 620, respectively, indicating an appreciable content (*ca.* 40%) of the rearranged alcohol (II; R = H). The product polymerised rapidly even at 0°.

A portion (0·2 g.) of the crude alcohol was esterified with *p*-phenylazobenzoyl chloride by the method described by Isler, Huber, Ronco, and Kofler (*Helv. Chim. Acta*, 1947, **30**, 1911). The crude ester was

purified by chromatographic adsorption on alumina (grade III—IV) and obtained as an oil which partly solidified when kept at −70° in contact with *n*-hexane–ethyl methyl ketone (20 : 1). The solid (30 mg.) was separated and recrystallised from acetone giving the *p-phenylazobenzoate* (13 mg.) as hygroscopic, pale orange microprisms, m. p. 114° (Found : C, 79·8; H, 6·95. $C_{25}H_{24}O_2N_2$ requires C, 79·8; H, 6·5%). Light absorption : see table.

1-cyclo*Hex*-1′-*enylhepta*-4 : 6-*dien*-1-*yn*-3-*ol* (IX).—A solution of penta-2 : 4-dien-1-al (14 g.) in ether (15 c.c.) was added during ½ hour with vigorous stirring to *cyclo*hexenylacetylenylmagnesium bromide (from 5·0 g. of magnesium and 25·0 g. of ethynyl*cyclo*hexene) in ether (650 c.c.). After the mixture had been stirred for a further 2 hours at 20°, the Grignard complex was decomposed by the addition of ammonium chloride (50 g.) in water (2 l.). Isolation of the product by means of ether gave the alcohol (22·5 g.) as a pale yellow oil, b. p. 90—95° (bath temp.)/10^{-3} mm., n_D^{21} 1·5566 (Found : C, 82·8; H, 8·8. $C_{13}H_{14}O$ requires C, 82·9; H, 8·55%). Light absorption : see table. The *α-naphthylurethane* crystallised from benzene–light petroleum (b. p. 40—60°) in micro-prisms, m. p. 191° (Found : C, 80·5; H, 6·3. $C_{24}H_{23}O_2N$ requires C, 80·65; H, 6·5%).

1-cyclo*Hexylheptan*-3-*ol and* 1-cyclo*Hexylheptan*-3-*one*.—The alcohol (IX) (2 g.) in methanol (50 c.c.) was shaken in hydrogen in the presence of a platinic oxide catalyst (10 mg.) until absorption was complete (1208 c.c. at 22°/769 mm.; equivalent to 4·8 double bonds). After removal of catalyst and solvent, distillation gave 1-cyclo*hexylheptan*-3-*ol* (1·7 g.) as a viscous oil, b. p. 87—88°/0·3 mm., n_D^{22} 1·4682 (Found : C, 79·3; H, 13·15. $C_{13}H_{24}O$ requires C, 78·8; H, 13·2%).

The alcohol (1·3 g.) was dissolved in glacial acetic acid (5 c.c.) and a solution of chromium trioxide (0·5 g.) in water (1 c.c.) and acetic acid (4 c.c.) was added dropwise. The mixture was kept at 20° for 15 hours and then diluted with water (15 c.c.). The product was isolated with ether and distilled giving 1-cyclo*hexylheptan*-3-*one* (1·2 g.), b. p. 110°/17 mm., n_D^{22} 1·4600 (Found : C, 79·0; H, 12·65. $C_{13}H_{24}O$ requires C, 79·5; H, 12·3%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in yellow needles, m. p. 97—98° (Found : N, 14·95. $C_{19}H_{28}O_4N_4$ requires N, 14·9%).

7-cyclo*Hex*-1′-*enylhepta*-2 : 4-*dien*-6-*yn*-1-*ol* (VIII).—A solution of (IX) (27·5 g.) in ether (150 c.c.) was shaken with dilute sulphuric acid (600 c.c.; 10% wt./vol.) and a trace of quinol for 24 hours. The ethereal solution was separated, washed with sodium hydrogen carbonate solution and water, and dried, and the solvent evaporated. The residue was extracted with light petroleum (500 c.c.; b. p. 40—60°), and the solution was filtered and the solvent evaporated yielding the crude re-arranged alcohol as a viscous oil (23 g.) which partly solidified on storage. Light absorption : maxima, 2290, 2800, and 2900 Å; $E_{1\,cm.}^{1\%}$ = 560, 920, and 920, respectively. Inflexion, 3000 Å; $E_{1\,cm.}^{1\%}$ = 730.

A portion (0·4 g.) of the crude alcohol was esterified with *p*-phenylazobenzoyl chloride (0·4 g.), by the method described by Isler, Huber, Ronco, and Kofler (*loc. cit.*), and the resulting ester was purified by chromatographic adsorption on alumina from a solution in light petroleum (b. p. 40—60°). The crude product (190 mg.) was recrystallised from acetone giving the *p-phenylazobenzoate* (150 mg.) as orange micro-prisms, m. p. 88° (Found : C, 78·45; H, 6·5. $C_{32}H_{28}O_2N_2$ requires C, 78·75; H, 6·1%). Light absorption : see table.

A solution of the crude alcohol (2 g.) in light petroleum (20 c.c.; b. p. 40—60°) was poured on to a column of partially deactivated alumina (50 g.; grade III), and the chromatogram developed with the same solvent (100 c.c.). The column was divided mechanically and elution of the two main bands with ether and methanol gave : (i) An oil (0·45 g.). Light absorption : maxima, 2280, 2800, and 2910 Å; $E_{1\,cm.}^{1\%}$ = 590, 1210, and 1540, respectively. Inflexion, 2650 Å; $E_{1\,cm.}^{1\%}$ = 810. A portion (0·2 g.) was distilled, giving 7-cyclo*hex*-1′-*enylhepta*-2 : 4-*dien*-6-*yn*-1-*ol* (0·1 g.) as a pale yellow viscous oil, b. p. 90° (bath temp.)/10^{-3} mm., n_D^{20} 1·6216 (Found : C, 82·9; H, 8·8. $C_{13}H_{14}O$ requires C, 82·9; H, 8·55%). Light absorption : see table. When kept at 0°, the alcohol solidified and was recrystallised from hexane giving pale yellow needles, m. p. 47—48°.

(ii) An oil (0·4 g.). Light absorption : maxima, 2280, 2800, 2940, and 3000 Å; $E_{1\,cm.}^{1\%}$ = 600, 1110, 1230, and 1120, respectively. Distillation of a portion (0·3 g.) gave an *isomer* (0·11 g.) of the alcohol as a pale yellow viscous oil, b. p. 90° (bath temp.)/10^{-3} mm., n_D^{20} 1·6130 (Found : C, 82·5; H, 8·9. $C_{13}H_{14}O$ requires C, 82·9; H, 8·55%). Light absorption : see table.

10-cyclo*Hex*-1′-*enyldeca*-3 : 5 : 7-*trien*-9-*yn*-2-*one* (VII).—A mixture of the alcohol (VIII) (13·7 g., crude), aluminium *tert.*-butoxide (18 g.), acetone (250 c.c.), and benzene (250 c.c.) was heated under reflux for 34 hours, cooled, and then poured into dilute sulphuric acid (750 c.c.; 10% wt./vol.) The organic layer was separated and the aqueous solution was extracted with ether. The combined ethereal extracts and benzene layer were washed with sodium hydrogen carbonate solution and water and dried. Evaporation of the solvents, finally at 50°/10^{-3} mm., gave a viscous oil (15·1 g.), n_D^{21} 1·6105. Light absorption : maxima, 2280, 2800—2900, and 3480—3650 Å; $E_{1\,cm.}^{1\%}$ = 625, 475, and 380, respectively. Inflexions, 2400 and 3080 Å; $E_{1\,cm.}^{1\%}$ = 430 and 350, respectively. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate as dark red needles, m. p. 181° (decomp.) (sinters at 176°) (Found : N, 13·45. $C_{25}H_{28}O_4N_4$ requires N, 13·8%). Light absorption in chloroform (main band only) : maximum, 4150 Å; ε = 51,000. An isomeric *derivative* was obtained from a specimen of the ketone made according to Heilbron, Jones, Lewis, Richardson, and Weedon (*J.*, 1949, 742) and crystallised from ethyl acetate–ethanol in dark red plates, m. p. 183° (decomp.) (Found : N, 13·75. $C_{25}H_{28}O_4N_4$ requires N, 13·8%). Light absorption in chloroform (main band only) : maximum. 4210 Å; ε = 46,500.

The crude ketone (5 g.) in alcohol (50 c.c.) was added to a solution of Girard reagent T (5 g.) (Girard and Sandulesco, *Helv. Chim. Acta*, 1936, **19**, 1095) in glacial acetic acid (5 c.c.), and the mixture heated under reflux for 1 hour. The mixture was cooled and poured into ice and water containing sodium hydrogen carbonate (7·35 g.). The non-ketonic fraction was extracted with ether. The aqueous

solution was acidified by the addition of sulphuric acid (110 c.c.; 50% wt./vol.) and set aside at 20° for 1 hour. Isolation with ether gave the crude ketone (1·75 g.) as a dark brown oil, n_D^{21} 1·622. Light absorption: maxima, 2280, 2640, and 3480 Å; $E^{1\%}_{1\,cm.}$ = 420, 375, and 900, respectively. A solution of the crude ketone in light petroleum (10 c.c.; b. p. 40—60°) and benzene (3 c.c.) was poured on to a column of alumina (35 g.; grade II—III), and the chromatogram developed with a mixture of the same solvents (150 c.c.). The least strongly adsorbed band was eluted with acetone, giving a dark brown oil (1·1 g.), n_D^{22} 1·6735. Light absorption: maxima, 2630 and 3510 Å; $E^{1\%}_{1\,cm.}$ = 420 and 1250, respectively, indicating an approximately 80% content of the ketone. Distillation of a portion of this material (0·2 g.) gave 10-cyclo*hex*-1′-*enyldeca*-3 : 5 : 7-*trien*-9-*yn*-2-*one* (0·13 g.) as a viscous orange oil, b. p. 130° (bath temp.)/5 × 10^{-4} mm., n_D^{19} 1·687 (Found: C, 84·95; H, 8·3. $C_{16}H_{18}O$ requires C, 84·9; H, 8·0%). Light absorption: see table. This ketone underwent no deterioration when kept at 0° for 2 weeks. The semicarbazone crystallised from methanol in yellow needles, m. p. *ca.* 198° (decomp.) (m. p. varied with the rate of heating). Light absorption in chloroform: maxima, 2650 and 3650 Å; ε = 9000 and 55,500, respectively. Inflexions, 3500 and 3800 Å; ε = 36,000 and 43,500, respectively [*idem, loc. cit.*, give m. p. 203° (decomp.). Light absorption in chloroform: maxima, 2650, 3640, and 3780 Å; ε = 8500, 59,500, and 46,500].

10-cyclo*Hex*-1′-*enyl*-2-*methyldeca*-1 : 3 : 5 : 7-*tetraen*-9-*yne*-1-*carboxylic Acid* (X) (with D. G. Lewis).—A mixture of the ketone (VII) (2·6 g.; crude) (Light absorption: maximum, 3500 Å; $E^{1\%}_{1\,cm.}$ = 1100), methyl bromoacetate (3·6 g.), benzene (50 c.c.), activated zinc turnings (1·8 g.), and mercuric chloride (0·05 g.) was heated under reflux with stirring for 45 minutes. The mixture was cooled and the benzene solution was then decanted from the small amount of unreacted zinc and shaken with dilute acetic acid (150 c.c.; 5% wt./vol.). The benzene layer was separated, washed free from acid, dried, and evaporated giving the crude hydroxy-ester as an orange-red oil (3·0 g.) which was heated with anhydrous oxalic acid (10 g.) for 2 hours at 100°/0·1 mm. The mixture was cooled and then extracted with light petroleum (b. p. 40—60°). The extract was washed free from acid, dried, and evaporated yielding the crude dehydrated ester as a viscous orange oil (1·7 g.). Light absorption: maxima, 2800, 3050, 3500, and 3670 Å; $E^{1\%}_{1\,cm.}$ = 530, 430, 490, and 550, respectively. Inflexions, 2530 and 2620 Å; $E^{1\%}_{1\,cm.}$ = 350 and 400, respectively.

The crude ester was hydrolysed by treatment with a 10% solution of potassium hydroxide in methanol for 48 hours at 20°. Isolation of the acidic product gave an orange gum (0·64 g.). Light absorption: maxima, 2280, 2820, 2910, and 3560 Å; $E^{1\%}_{1\,cm.}$ = 520, 350, 350, and 370, respectively. Methanol (5 c.c.) was added to the gum, and the mixture kept at 0° for 3 days during which time a small amount of solid was deposited. Recrystallisation of the latter from methanol yielded the *acid* as yellow prisms (20 mg.), m. p. 210—215° (decomp.) (Found: C, 80·4; H, 8·7. $C_{18}H_{20}O_2$ requires C, 80·6; H, 7·5%). Light absorption: see table.

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Light-absorption data were determined by Dr. E. A. Braude.

Imperial College of Science and Technology,
London, S.W.7.

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686. *The Synthesis of* 8-iso*Amyl-5-hydroxy-7-methoxy-2 : 2-dimethylchroman, a Degradation Product of Osajin and Pomiferin.*

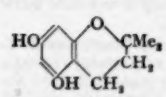
By E. K. Pierpoint, Alexander Robertson, and W. B. Whalley.

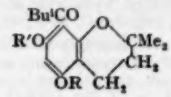
Prepared from *iso*butyl cyanide and 5 : 7-dihydroxy-2 : 2-dimethylchroman (I), the 8-*iso*valeroyl compound (II; R = R′ = H) was converted by successive monobenzylation and methylation into the 5-benzyloxy- (II; R = CH_2Ph, R′ = H) and the 5-benzyloxy-7-methoxy- (II; R = CH_2Ph, R′ = Me) chroman, respectively. Reduction of the latter, followed by debenzylation furnished 8-*iso*amyl-5-hydroxy-7-methoxy-2 : 2-dimethylchroman (III), identical with a degradation product of osajin and pomiferin.

By the hydrolytic fission of tetrahydro-osajin dimethyl ether and of tetrahydropomiferin trimethyl ether, Wolfrom *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 406) obtained small amounts of a compound which they characterised as the 3 : 5-dinitrobenzoate, and considered to be 8-*iso*amyl-5-hydroxy-7-methoxy-2 : 2-dimethylchroman (III).

In an investigation on chromans (unpublished work) we had occasion to prepare 5 : 7-dihydroxy-2 : 2-dimethyl-8-*iso*valeroylchroman (II; R = R′ = H) and from this compound have now synthesised the degradation product (III).

The application of the Hoesch ketone synthesis to 5 : 7-dihydroxy-2 : 2-dimethylchroman (I) with *iso*butyl cyanide gave predominantly the 8-*iso*valeroylchroman (II; R = R′ = H), together with a small quantity of the isomeride, 5 : 7-dihydroxy-2 : 2-dimethyl-6-*iso*valeroyl-


(I)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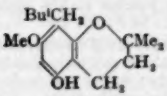
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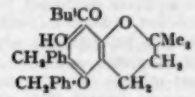
(IV)

chroman (cf. the use of methyl cyanide in this reaction by Backhouse and Robertson, *J.*, 1939, 1257). Benzylation of (II; R = R′ = H) gave rise to a monobenzyl ether, having a positive ferric reaction, together with small amounts of a compound which is regarded as the *C*-benzylated derivative (IV). Methylation of the monobenzyl ether followed by debenzylation of the product furnished a monomethyl ether readily soluble in dilute aqueous sodium hydroxide and having a negative ferric reaction. Consequently, by analogy with 5 : 7-dihydroxy-8-β-phenylpropionylchroman (Backhouse and Robertson, *loc. cit.*), it is clear that the parent ketochroman has the structure (II; R = R′ = H) now assigned and hence its *O*-monomethyl derivative is 5-hydroxy-7-methoxy-2 : 2-dimethyl-8-*iso*valeroylchroman (II; R = H; R′ = Me). The isomeride formed in small quantity with (II; R = R′ = H) is, therefore, 5 : 7-dihydroxy-2 : 2-dimethyl-6-*iso*valeroylchroman.

Attempts to reduce the methyl ether (II; R = H, R′ = Me) by Clemmensen's method were unsuccessful and only amorphous products were obtained. By the same method, however, 5-benzyloxy-7-methoxy-2 : 2-dimethyl-8-*iso*valeroylchroman (II; R = CH_2Ph, R′ = Me) gave 8-*iso*amyl-5-benzyloxy-7-methoxy-2 : 2-dimethylchroman and on debenzylation this compound furnished 8-*iso*amyl-5-hydroxy-7-methoxy-2 : 2-dimethylchroman (III), which was characterised by the formation of the 3 : 5-dinitrobenzoate, identical in every way (including the infra-red absorption spectra) with a natural specimen kindly provided by Professor M. L. Wolfrom.

Experimental.

5 : 7-*Dihydroxy*-2 : 2-*dimethyl*-8-iso*valeroylchroman* (II; R = R′ = H).—A solution of *iso*butyl cyanide (1·5 g.) and 5 : 7-dihydroxy-2 : 2-dimethylchroman (Bridge, Heyes, and Robertson, *J.*, 1937, 279) (3 g.) in ether (60 ml.), containing powdered zinc chloride (2·5 g.), was saturated at 0° with hydrogen chloride, and 5 days later the crystalline ketimine complex was isolated. The combined product from five experiments was heated on the steam-bath for 5 hours with water (50 ml.) and after the aqueous layer had been decanted the brown semi-solid residue was washed with ether, giving a colourless solid, m. p. 286° (decomp.); a further small quantity of this product was deposited by the cooled aqueous extract. A solution of this compound (6 g.) in a mixture of water (100 ml.) and ethanol (40 ml.) was heated under reflux for 5½ hours, the cooled hydrolysate was repeatedly extracted with ether, the dried extracts were evaporated, and the residual gum was crystallised from light petroleum (b. p. 60—80°), giving 5 : 7-*dihydroxy*-2 : 2-*dimethyl*-8-iso*valeroylchroman* (3 g.) in pale greenish-yellow plates, m. p. 138° (Found : C, 68·8; H, 8·2. $C_{14}H_{22}O_4$ requires C, 69·1; H, 7·9%). This compound, which gives an intense dark violet coloration with alcoholic ferric chloride, is readily soluble in methanol, ethanol, ethyl acetate, benzene, or 1% aqueous sodium hydroxide, and almost insoluble in cold petroleum or water. It does not form an oxime or 2 : 4-dinitrophenylhydrazone under the usual conditions.

Evaporation of the ethereal washings of the crude ketimine complex, and purification of the residue from light petroleum (80—100°), gave a small and variable yield of 5 : 7-*dihydroxy*-2 : 2-*dimethyl*-6-iso*valeroylchroman* in almost colourless needles, m. p. 144—145° (Found : C, 68·9; H, 7·9%). An ethanol solution of this ketone exhibited a purple coloration with ferric chloride, and a mixture with the isomeric ketone had m. p. 110°.

5-*Benzyloxy*-7-*hydroxy*-2 : 2-*dimethyl*-8-iso*valeroylchroman*.—Prepared by the interaction of 5 : 7-dihydroxy-2 : 2-dimethyl-8-*iso*valeroylchroman (2 g.), benzyl bromide (1·3 g.), and anhydrous potassium carbonate (3 g.) in boiling acetone (100 ml.) during 2 hours and purified by fractional crystallisation from methanol, 5-*benzyloxy*-7-*hydroxy*-2 : 2-*dimethyl*-8-iso*valeroylchroman* (1·4 g.) was obtained in prisms or plates, m. p. 92—93°, insoluble in 1% aqueous sodium hydroxide and having a purple ferric reaction in alcohol (Found : C, 74·8; H, 7·6. $C_{23}H_{28}O_4$ requires C, 75·0; H, 7·6%). The impurity associated with this ether was much less soluble in methanol and appeared to be 6-*benzyl*-5-*benzyloxy*-7-*hydroxy*-2 : 2-*dimethyl*-8-iso*valeroylchroman* which separated in long, thin, pale greenish prisms, m. p. 117° (Found : C, 77·9; H, 7·2. $C_{30}H_{34}O_4$ requires C, 78·6; H, 7·4%). This compound was readily soluble in cold light petroleum (b. p. 60—80°), and gave an olive green ferric reaction in alcohol.

5-*Hydroxy*-7-*methoxy*-2 : 2-*dimethyl*-8-iso*valeroylchroman*.—Prepared by the interaction of 5-benzyloxy-7-hydroxy-2 : 2-dimethyl-8-*iso*valeroylchroman (2 g.), excess of methyl iodide, and potassium carbonate (3 g.) in boiling acetone (100 ml.) during 60 hours, 5-*benzyloxy*-7-*methoxy*-2 : 2-*dimethyl*-8-iso*valeroylchroman* separated from aqueous methanol in rectangular prisms (1·9 g.), m. p. 90—91°, soluble in the usual organic solvents except light petroleum, insoluble in 2*N*-sodium hydroxide, and having a negative ferric reaction in alcohol (Found : C, 75·1; H, 7·5. $C_{24}H_{30}O_4$ requires C, 75·4; H, 7·9%).

A solution of the foregoing keto-chroman (1 g.) in acetic acid (60 ml.), containing a palladium–charcoal catalyst (from 1 g. of charcoal and 20 ml. of 1% aqueous palladium chloride), was shaken with hydrogen until the absorption of gas had ceased (*ca.* 20 minutes). On isolation the resulting *5-hydroxy-7-methoxy-2 : 2-dimethyl-8-isovaleroylchroman* (0·6 g.) formed small needles, m. p. 142—143°, from dilute methanol, readily soluble in 1% aqueous sodium hydroxide and having a negative ferric reaction in alcohol (Found: C, 69·9; H, 7·9. $C_{17}H_{24}O_4$ requires C, 69·9; H, 8·2%).

8-iso*Amyl-5-hydroxy-7-methoxy-2 : 2-dimethylchroman.*—A mixture of 5-benzyloxy-7-methoxy-2 : 2-dimethyl-8-*iso*valeroylchroman (0·5 g.), zinc amalgam (12 g.), hydrochloric acid (8 ml.), water (12 ml.), and toluene (20 ml.) was heated under reflux for 5 hours, the toluene layer was separated, and the aqueous liquors were extracted with ether. Evaporation of the combined toluene–ether solution gave 8-iso*amyl-5-benzyloxy-7-methoxy-2 : 2-dimethylchroman* (0·4 g.) which separated from methano in hexagonal plates, m. p. 59—60° (Found: C, 77·9; H, 9·0. $C_{24}H_{32}O_3$ requires C, 78·3; H, 8·7%). This chroman (1·5 g.) was debenzylated with hydrogen and a palladium–charcoal catalyst (from 1 g. of charcoal and 20 ml. of 1% palladium chloride solution) in acetic acid. Evaporation of the filtered solution left a colourless gum which, on crystallisation from light petroleum (60—80°), gave 8-*iso*amyl-5-hydroxy-7-methoxy-2 : 2-dimethylchroman in plates (*ca.* 0·6 g.), m. p. 86°, having a negative ferric reaction in alcohol (Found: C, 73·5; H, 9·2. Calc. for $C_{17}H_{26}O_3$: C, 73·4; H, 9·4%). Prepared by the pyridine method, the 3 : 5-dinitrobenzoate separated from aqueous ethanol in golden leaflets, m. p. 131°, identical with the natural specimen (Found: C, 61·0; H, 5·9; N, 5·9. Calc. for $C_{24}H_{28}O_8N_2$: C, 61·1; H, 6·0; N, 6·0%).

UNIVERSITY OF LIVERPOOL. [*Received, August 8th*, 1951.]

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687. *The Effect of Structure of Diacyl Peroxides on the Rates of Initiation of the Polymerisation of Styrene.*

By W. COOPER.

The rates of initiation of the polymerisation of styrene by 74 diacyl peroxides have been determined. The rates of initiation by substituted dibenzoyl peroxides were increased by electron-releasing groups and decreased by electron-attracting groups. *o*-Substituents greatly accelerated the rate because of a combination of steric and polarisation effects.

Straight-chain, saturated, aliphatic diacyl peroxides showed little difference amongst themselves in initiation rate, but those possessing a radical of the allyl type decomposed very rapidly; steric effects, too, were important in some cases. The rates of initiation by unsymmetrical diacyl peroxides were intermediate between the rates found for the two symmetrical peroxides.

The primary thermal decomposition rates of substituted dibenzoyl peroxides show the same trend with changes in polarity of the substituent, and it is suggested that they may be identified with the rates of initiation of polymerisation. Preliminary results show that this is probably not so in the case of the aliphatic diacyl peroxides.

THE decomposition of organic peroxides in the pure state and in solution has attracted much attention in recent years. Most studies have dealt with the mechanism of the reactions involved, and where rates of decomposition have been determined the usual analytical methods have been employed.

The rates of polymerisation of vinyl monomers may be used to calculate the primary thermal decomposition rate of the peroxide provided that the following conditions are satisfied: (*a*) The radical-induced decomposition of the peroxide should not alter the free-radical concentration of the system, and thus not affect the reaction rate. (*b*) The radicals from the peroxide must be of activity comparable with, or greater than, those derived from the monomer. (*c*) The value of k_t/k_p^2 must be known (k_p and k_t are the velocity coefficients for chain growth and for termination, respectively, in the polymerisation reaction). (*d*) The thermal polymerisation rate of the monomer, if not negligible in comparison with the catalysed rate, must be known. (*e*) There is no decomposition of the peroxide by reactions not involving free radicals.

Since the radical-induced decomposition is a transfer reaction there is no reason to believe that it changes the free-radical concentration. The radicals formed from the peroxide in the primary decomposition (A) have the same structure as those from the induced decomposition (B): hence they will possess comparable activities. It will be shown in a paper dealing with

effect of peroxide structure on the radical-induced decomposition, that most peroxides produce radicals of greater activity than those from styrene.

$$(R{\cdot}COO)_2 \longrightarrow 2R{\cdot}CO{\cdot}O{\cdot} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$

$$(R{\cdot}COO)_2 + R' \longrightarrow R{\cdot}CO{\cdot}OR' + R{\cdot}CO{\cdot}O{\cdot} \quad . \quad . \quad . \quad . \quad . \quad . \quad (B)$$

Two reactions which would result in the disappearance of peroxide without influencing the polymerisation are ionic fission of the peroxide link (Leffler, *J. Amer. Chem. Soc.*, 1950, **72**, 67) and loss of peroxide as a result of some of the acyloxy-radicals recombining to form inactive products before separating sufficiently to attack the monomer. It should be possible, however, to establish whether or not these reactions are of consequence by comparison with the published data.

The above conditions being assumed to be satisfied, the rate (k_i) of initiation of polymer chains will be the same as the rate of primary decomposition. It will be related to the overall first-order velocity " constant " (k_d) by

$$k_d = k_i + k'c^x$$

where $x = 0$—$1{\cdot}0$,* k' is a constant depending on the rate of the radical-induced reaction (B), and c is the concentration of the catalyst.

TABLE I.†

Symmetrically substituted dibenzoyl peroxides.

Substituent	10^4R_d	10^4k_i	Subst.	10^4R_d	10^4k_i	Subst.	10^4R_d	10^4k_i
(H)	1·265	7·0	—	—	—	—	—	—
o-Me	2·515	27·8	*m*-Me	1·165	6·0	*p*-Me	1·570	10·9
o-OMe	5·57	138	*m*-OMe	1·430	9·0	*p*-OMe	2·050	18·5
o-OEt	5·20	119	—	—	—	*p*-OEt	2·060	18·6
o-F	1·520	10·1	*m*-F	0·910	3·6	*p*-F	1·100	5·3
o-Cl	2·580	28·2	*m*-Cl	0·910	3·6	*p*-Cl	1·110	5·4
o-Br	4·420	85	*m*-Br	0·925	3·8	*p*-Br	1·090	5·2
o-I [a]	0·026	0·11	*m*-I	0·910	3·6	*p*-I	1·110	5·4
o-NO_2	0·417	(0·8)	*m*-NO_2	0·380	(0·7)	*p*-NO_2	0·215	(0·2)
						p-Et	1·495	9·9
o-CO_2Me	1·520	10·1	—	—	—	*p*-CH_2:CH	1·215	6·5
o-O·CH_2Ph	5·20	119	—	—	—	*p*-Pr^i	1·545	10·6
						p-Bu^t	1·695	12·7
3 : 5-Me_2	1·315	7·7	3 : 4-$(OMe)_2$	1·420	8·9	*p*-Ph	1·390	8·5
2 : 3-C_4H_4 [b]	7·20	229	2 : 3-$(OMe)_2$	3·31	48	*p*-*n*-$C_8H_{17}O$	2·030	18·2
3 : 4-C_4H_4 [c]	1·330	7·8	3 : 4-CH_2O_2	0·785	2·7	*p*-OAc	1·200	6·0
3 : 5-$(NO_2)_2$	0	—	2 : 3 : 4 : 5-Cl_4	1·390	8·5	*p*-O·CO_2Me	1·165	6·3
6-Cl, 3-NO_2	0·44	(0·9)	—	—	—	*p*-CN	0·900	3·6

† Geneva notation (CO_2H = 1) is used for aliphatic acids (except propionic and butyric).

Aliphatic diacyl peroxides.

Peroxide	10^4R_d	10^4k_i	Peroxide	10^4R_d	10^4k_i
Diacetyl	2·14	20·2	Dihexa-2 : 4-dienoyl	2·35	24·3
Dibutyryl	2·08	19·1	Diundec-9-enoyl	2·08	19·1
Di*iso*butyryl	9·10	364	Dioleoyl	1·84	14·9
Dihexanoyl	2·06	18·6	Bis-$\beta\gamma$-dibromobutyryl	6·45	183
Bishexahydrobenzoyl [d]	2·62	68·5	Bis-9 : 10-dibromoundecanoyl	2·00	17·6
Dioctanoyl	2·17	20·8	Bis-9 : 10-dibromostearoyl	1·85	15·1
Dilauroyl	2·06	18·6	Bisphenylacetyl [a]	0·077	0·95
Dimyristoyl	2·06	18·6	Di-γ-phenyl propionyl	2·16	20·5
Dipalmitoyl	1·88	15·6	Dicinnamoyl	1·92	16·2
Distearoyl	1·84	14·9	Di-*p*-methoxycinnamoyl	2·08	19·1
Dibut-2-enoyl	2·53	28·2	Di-*p*-nitrocinnamoyl	0·405	(0·7)
Dibut-3-enoyl [e]	0·35	6·3	Di-5-phenylpenta-2 : 4-dienoyl	0·44	0·85

Unsymmetrical diacyl peroxides.

Peroxide	10^4R_d	10^4k_i	Peroxide	10^4R_d	10^4k_i
Benzoyl *p*-nitrobenzoyl	0·530	1·2	Benzoyl stearoyl	1·750	13·5
Benzoyl *m*-nitrobenzoyl	0·725	2·3	Adipoyl dibenzoyl [f]	1·265	7·0
Acetyl benzoyl	1·940	16·5	Dibenzoyl phthaloyl [f]	1·350	8·0

[a] 0° ($K = 1{\cdot}4 \times 10^4$). [b] Di-1-naphthoyl peroxide. [c] Di-2-naphthoyl peroxide. [d] 50° ($K = 1{\cdot}0 \times 10^3$). [e] 20° ($K = 4{\cdot}6 \times 10^3$). [f] Examined at 0·007 mole/l. to give the same active oxygen concentration as the other peroxides.

* The value of this exponent depends on the mechanisms assumed for the induced decomposition and termination reactions. For most peroxides in styrene, termination and transfer reactions mainly involve monomer radicals, and hence $x = 0{\cdot}5$.

The relation between k_i and the rate of polymerisation (R_c) is

$$k_i = k_i(R_c^2 - R_T^2)/2k_p^2M^2C$$

where R_T is the rate of thermal polymerisation, and M and C are the concentration of monomer and catalyst at any time.

Under constant conditions of temperature and catalyst concentration, and at the start of the reaction

$$k_i = K(R_c^2 - R_T^2)$$

In this work, $K = 440$ l.^{2} mole^{-2} sec.$^{-1}$. The temperature used was 70°, and the value of k_i/k_p^2 calculated from Bamford and Dewar's data (*Faraday Soc. Discuss.*, 1947, **2**, 313) was 850 mole l.$^{-1}$ sec.$^{-1}$. The catalyst and monomer concentrations were 0·014 and 8·28 mole/l., respectively. The value of R_T was $0{\cdot}55 \times 10^{-5}$ mole l.$^{-1}$ sec.$^{-1}$ at 70°, and was thus negligible in comparison with the reaction rates measured in this work.

Table I gives data for a number of peroxides. Some of the peroxides were so unstable that they had to be examined at temperatures below 70°; these have been indicated in the table and the appropriate values of K have been used for the calculation of k_i.

TABLE II.

	Dibenzoyl		Di-1-naphthoyl			Dibenzoyl		Di-1-naphthoyl	
Temp.	10^4R_c	10^4k_i	10^4R_c	10^4k_i	Temp.	10^4R_c	10^4k_i	10^4R_c	10^4k_i
40° [a]	0·063	0·061	0·340	2·34	60° [b]	0·480	1·43	2·660	42·8
50	0·180	0·32	1·060	11·2	70	1·265	7·0	7·20	229
	$E_i = 33{\cdot}6$ kcals./mole.					$E_i = 32{\cdot}0$ kcals./mole.			
	$A_i = 2 \times 10^{16}$.					$A_i = 6 \times 10^{16}$.			
	[a] $K = 1{\cdot}54 \times 10^3$.					[b] $K = 620$.			

The energy of activation for the decomposition (E_i) and the frequency factor (A_i) of dibenzoyl and di-1-naphthoyl peroxides were determined from measurements of k_i at different temperatures. The results are given in Table II.

DISCUSSION.

Substituted Dibenzoyl Peroxides.—With *m*- and *p*-substituents the results show that electron-releasing groups increase the rate of initiation by the peroxides and that the reverse effect occurs with electron-attracting groups. A plot of log $(k_i)_X/(k_i)_H$, where $(k_i)_X$ and $(k_i)_H$ are respectively the initiation rates for the substituted and the unsubstituted peroxide, against Hammett's σ factors ("Physical Organic Chemistry," McGraw Hill, 1940, p. 188) for the substituents shows clearly the influence of their polarity, though there are some irregularities (see Fig. 1).

The best line relating the data (calculated by the method of least squares) gives a value for ρ of $-0{\cdot}38$ in Hammett's equation $\log (k_i)_X/(k_i)_H = \sigma\rho$. This result is identical with that found by Swain, Stockmayer, and Clarke (*J. Amer. Chem. Soc.*, 1950, **72**, 5426), though their experimental conditions were very different. It supports the view that variations in decomposition rate result from changes in the peroxide structure and are independent of the solvent. A comparison of some of the values obtained in this investigation with those calculated from published data is given in Table III. Except where indicated, the results are from those of

TABLE III.

	$k_i \times 10^5$ (sec.$^{-1}$)		$k_d \times 10^5$ (sec.$^{-1}$)
Substituent	Published data	This investigation	
p-Methoxy	34·6	18·5	—
p-Methyl	18·0	10·9	—
p-*tert.*-Butyl	17·9	12·7	—
m-Methyl	12·9	6·0	—
Unsubstituted	12·3, 8·2 (B),[a] 8·7 (S),[a] 8·1 (S)[f]	7·0	9·9 (B),[a] 9·8 (B),[d] 9·7 (B),[b] 9·7 (B),[c] 11·4 (B),[e] 9·1 (S)[f]
p-Chloro	10·6	5·4	6·4 (B),[c] 10·3 (S)[g]
p-Bromo	9·5	4·2	—
m-Bromo	7·6	3·8	7·6 (B)[g]
p-Cyano	6·0	3·6	—
2 : 3-C_4H_4	—	229	232 (B)[b]

[a] Bartlett and Nozaki, *J. Amer. Chem. Soc.*, 1946, **68**, 1686. [b] Author, unpublished results. [c] Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 1208. [d] Hartmann, Sellars, and Turnbull, *ibid.*, 1947, **69**, 2416. [e] Cuthbertson, McClure, and Robertson, *Canad. J. Res.*, 1942, **20**, 103. [f] Mayo, Gregg, and Matheson, *J. Amer. Chem. Soc.*, 1951, **73**, 1691. [g] Redington, *J. Polymer. Sci.*, 1948, **3**, 503.

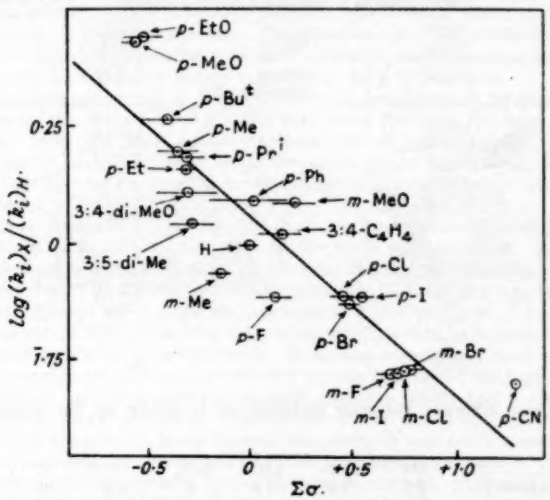
Swain *et al.* (*loc. cit.*), who used dioxan as the solvent. In the other cases the solvent is noted (B = benzene; S = styrene).

It is seen that the results observed for dioxan solutions are considerably higher than those found with other solvents or those from the polymerisation experiments. The differences could result from several causes: (*a*) The use of too low a value of k_i/k_p^2 in the calculation of k_i from polymerisation experiments. (*b*) Intrinsically higher values of k_i in the ether-type solvent. (*c*) Incomplete suppression of the chain decomposition reaction. Most of the data on dibenzoyl peroxide show that the overall decomposition rate in benzene or styrene, which includes a substantial (*ca.* 10%) term due to the induced reaction, is less than was found by Swain *et al.* (*loc. cit.*) in dioxan solution for the primary decomposition. Similar conclusions could be reached from the relative values for the di-*p*-chloro- and di-*m*-bromo-benzoyl peroxides.

There is no reason to doubt that the chain decomposition was inhibited in the decomposition reactions in dioxan, although the quoted values for E_i are somewhat low. The dielectric

FIG. 1.*

The horizontal lines through the points show the possible errors in the determination of $\Sigma\sigma$ (*Hammett*, loc. cit.). *The value for the* p-*cyano-grouping is that found by Roberts and McElhill* (J. Amer. Chem. Soc., 1950, **72**, 628).



* *The prefix "di" (or "bis") is omitted throughout in the lettering.*

constant of the solvent (2·214 at 80·1°; Vaughan, *Phil. Mag.*, 1939, **27**, 669) does not suggest the likelihood of an ionic decomposition reaction of the type described by Leffler (*loc. cit.*). [The overall decomposition rate of dibenzoyl peroxide in nitrobenzene is sufficiently close to that found in benzene to indicate that ionic decomposition is of little significance (Brown, *loc. cit.*).] It would seem, therefore, that the values of k_i are affected to some extent by the solvent. The value for k_i found by Mayo *et al.* (*loc. cit.*) is comparable with that found in this investigation, and is also a measure of the peroxide actually initiating polymerisation. Mayo, however, concludes that the actual values of k_i may be higher than those found by polymerisation experiments and raises the possibility that its value may depend on the solvent used. By comparison with the results of Bartlett and Nozaki and of Mayo, the results found here would appear to be 15—25% low. This variation is quite reasonable in view of the uncertainty of the absolute values of the velocity constants of the polymerisation reaction. It is concluded that, provided that the limitations of the method are realised, the determination of k_i gives a satisfactory measure of the primary decomposition reaction.

The effect of changes in polarity is in the reverse direction to that found for the alkyl hydroperoxides and dialkyl peroxides, where the stability increases with increase in the electron-

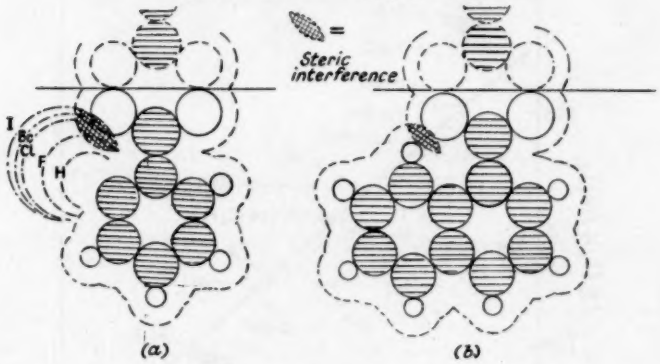
releasing character of the alkyl group. Walsh (*J.*, 1948, 331) has suggested that, although electron release would strengthen the O–O bond, too great a transfer of electron density could, by extensive overlap of the atomic orbitals, actually weaken the bond. This explanation may apply to the aromatic diacyl peroxides, but other causes may also be operative; for example, resonance stabilisation of the peroxide molecule and the radicals derived from it may be affected differently by a given substituent.

Measurements have not been made to determine whether substituents greatly influence the strength of the O–O bond. Davison (in the press) has shown that with the peroxides there is an increase in the strength of the adjacent carbonyl bond with increase in the electron-attracting character of the substituent, but it is not possible to say whether this would be accompanied by the opposite effect on the strength of the peroxide link.

The methyl group accelerates the decomposition in all orientations. As it is electron-attractive in the *m*-position, its effect, though small, is not in the expected direction. It is significant, however, that with the 2 : 3- and 3 : 4-dimethoxy-substituted peroxides, the *m*-group reduces the influence of the electron-releasing *o*- or *p*-groups.

FIG. 2.

Steric effects in o-substituted diacyl peroxides.



Steric effects can influence peroxide stability, as is shown by the pronounced effect of *o*-substituents:

Substituent	Me	MeO	EtO	NO_2	F	Cl	Br	I [a]
Ratio of k_1, *ortho*/*para*	2·7	7·4	6·4	4	1·9	5·2	16·3	*ca.* 10^3

The ratio of k_1 for di-1- and di-2-naphthoyl peroxides was 29·4.
[a] Estimated from the determination at 0°.

In the case of the halogens, the relation between decomposition rate and the size of the atom is readily seen, and a diagram of the molecular outlines (Fig. 2, *a*) shows considerable interference with the rotation of the molecule. The figure was constructed from the values found by Kassatochkin, Perlina, and Ablesovo (*Compt. rend. Acad. Sci. U.R.S.S.*, 1945, **47**, 36). Their results would imply that the four oxygen atoms in the peroxide are equivalent [in a similar way to the equivalence of the four sulphur atoms in tetramethylthiuram disulphide (Craig, Davidson, Juve, and Geib, *J. Polymer Sci.*, 1951, **6**, 1)], and, therefore, that steric hindrance would be in the rotation of the aryl group about the C–C bond and not rotation of the acyloxy-group about the C–O bond. It should be pointed out, however, that the data on the structure of dibenzoyl peroxide require further confirmation. They are not consistent with the infra-red spectrum; moreover, recent (unpublished) work by Dr. I. H. Riley has shown that their interpretation of the *X*-ray crystallographic data is open to question.

The almost identical effects of the methoxy-, ethoxy-, and benzyloxy-groups in the *o*-position show that only the atoms close to the ring influence the stability; attempts to prepare a peroxide with the bulky *o*-methylthio-group were unsuccessful. Size, however, is not the only factor since the methyl group has a much smaller effect than the comparably sized iodine

atom. The introduction of a second substituent markedly affects the influence of the *o*-group. This is true for many reactions where steric considerations are important (Adams and Snyder, *J. Amer. Chem. Soc.*, 1938, **60**, 1411), though in these decompositions it is not possible to differentiate between the steric and the polarisation effects. The rapid rate of decomposition of di-1-naphthoyl peroxide may thus be attributed to the rigidity of the ring structure, since the interference is relatively small (Fig. 2, *b*).

Examination of the values for the nitro-substituted peroxides shows them to be anomalously low. This is undoubtedly due to their forming radicals of low activity which inhibit the polymerisation reaction. Confirmation of this was the fall-off from linearity between the rate of polymerisation and the square root of the catalyst concentration with nitro-substituted peroxides (Cooper, *Nature*, 1948, **162**, 927). Introduction of a second nitro-substituent lowered the activity further, and bis-3 : 5-dinitrobenzoyl peroxide completely inhibited polymerisation.

A result for which no satisfactory explanation was found was the very low reaction rate of di-3 : 4-methylenedioxybenzoyl peroxide. The grouping has a normal electron-releasing character, and it would be expected to give a rate similar to that of the corresponding dimethoxy-compound. The peroxide itself had a higher melting point and was less soluble than the other alkoxy-substituted peroxides.

Di-*p*-vinylbenzoyl peroxide was peculiar in that it was copolymerised into the polymer chain. Initially a soluble, highly branched polymer was formed which contained peroxide groups; when heated, it became insoluble. The peroxide itself polymerised in the solid state or in solution to an infusible. insoluble polymer. However, the rate of fission of the peroxide link was not greatly affected by its incorporation into the polymer chain.

The temperature-dependence of k_i gave a value of E_i for dibenzoyl peroxide in good agreement with values in the literature; *e.g.*, 33·3 kcal./mole (benzene) (Nozaki and Bartlett, *J. Amer. Chem. Soc.*, 1946, **68**, 1686). The increased rate of decomposition of di-1-naphthoyl peroxide results partly from an increase in the frequency factor (brought about by steric strain in the molecule), but also by a reduction in the energy of activation which is, no doubt, due to a polarisation effect.

Aliphatic Diacyl Peroxides.—The straight-chain, saturated diacyl peroxides decomposed at roughly the same rate, with a slight fall as the series was ascended. Groupings distant from the peroxide linkage had little effect on the rate, but double bonds showed a pronounced effect if they formed part of a $\cdot CH{:}CH\cdot CH_2\cdot CO\cdot$ grouping. When this was the case the effect was very marked; dibut-3-enoyl peroxide decomposed about 50 times as fast as the isomeric dibut-2-enoyl peroxide. The reason for this would be that the large resonance stabilisation of the allyl radical facilitates decomposition. A similar comparison may be made between bisphenylacetyl peroxide, which decomposed very rapidly because of the high resonance energy of the benzyl radical, and di-(γ-phenylpropionyl) peroxide which had a stability similar to that of an *n*-aliphatic diacyl peroxide. These observations would suggest that the free alkyl radicals were formed directly by breakdown of the peroxide and not by unimolecular decomposition of an acyloxy-radical. In support of this, it is significant that in the decomposition of aliphatic diacyl peroxides carbon dioxide is always formed, whereas with the aromatic diacyl peroxides such formation can be largely suppressed by the use of suitable conditions.

There are fewer data on the decomposition of aliphatic diacyl peroxides for comparison with the k_i values; some results are given below—they are calculated for 70°, except for the phenylacetyl peroxide (C = carbon tetrachloride, T = toluene).

Peroxide	10^4k_i	10^4k_d	Peroxide	10^4k_i	10^4k_d
Diacetyl	20·2	14·5 (C),[a] 19·0 (T) [b]	Di-(γ-phenylpropionyl)	20·5	55 (S) [d]
Dilauroyl	18·6	52 (S) [c]	Bisphenylacetyl (0°)	(1·0)	28 (T) [c]

[a] Edwards and Mayo, *J. Amer. Chem. Soc.*, 1950, **72**, 1265. [b] Ross and Fineman, *ibid.*, 1951, **73**, 2176. [c] Redington, *loc. cit.* [d] Author, unpublished result. [e] Leffler and Bartlett, *J. Amer. Chem. Soc.*, 1950, **72**, 3030.

It will be shown in a subsequent paper that these *n*-aliphatic diacyl peroxides do not react appreciably with the monomer radicals. Thus a large proportion of the dilauroyl and di-(γ-phenylpropionyl) peroxides decomposing must do so by non-radical reactions. Bisphenylacetyl peroxide apparently gives radicals of low activity, and consequently there is no relation between k_i and k_d. It is possible that some ionic breakdown of the catalyst occurs, as suggested by Leffler and Bartlett (*loc. cit.*), and some is consumed in terminating polymer chains, but the rate-determining step in the polymerisation must be the slow reaction between benzyl radicals and styrene. Conjugated double bonds, including conjugation with the carbonyl bond, had

a relatively small effect. Di-(5-phenylpenta-2 : 4-dienoyl) peroxide was an apparent exception to this, but here the great resonance stabilisation would result in radicals of low reactivity, which would be inefficient in initiating polymerisation.

Steric influences apparently are important in the aliphatic series also, as shown by the rapid decomposition rate of bishexahydrobenzoyl peroxide, and of those peroxides with a methyl or a bromo-substituent adjacent to the carbonyl group. In general, apart from these cases and those where resonance-stabilised radicals may be formed, most aliphatic diacyl peroxides decomposed at substantially the same rate. Their structure, however, greatly affected their participation in the radical-induced decomposition reaction, as will be shown in another paper.

The decomposition rates of the saturated aliphatic diacyl peroxides and dibut-2-enoyl peroxide, when compared with the dissociation constants of the corresponding acids, indicate a trend in the reverse direction to that found for the aromatic diacyl peroxides. Bischloroacetyl peroxide, derived from a strong acid, has also been found to decompose very rapidly (Price, Kell, and Krebbs, *J. Amer. Chem. Soc.*, 1942, **64**, 1103).

Unsymmetrical Diacyl Peroxides.—These compounds require little comment. In all cases they had rates of decomposition intermediate between those of the two corresponding symmetrical ones. The two compounds containing two peroxide links in the molecule did not possess any unusual properties. Dibenzoyl phthaloyl peroxide decomposed at roughly the same rate as the similarly constituted di-*o*-carbomethoxybenzoyl peroxide, and the proximity of the two peroxide links did not appear to influence its stability.

Experimental.

Preparation of Organic Peroxides.—Most of the diacyl peroxides were prepared from the acyl chlorides and sodium peroxide solution. Some of the aromatic diacyl peroxides were readily hydrolysed or contained groupings attacked by alkali [*e.g.*, bis-3 : 5-dinitrobenzoyl peroxide and di-(*p*-methyl carbonatobenzoyl) peroxide]. In these cases the most effective reagent was 30% hydrogen peroxide and sodium hydrogen carbonate, which gave high yields of peroxide. Diacetyl peroxide was prepared by Gambarjam's method (*Ber.*, 1909, **42**, 4008). An alternative method, suitable for the preparation of small amounts of this peroxide, was to mix equal volumes of strongly cooled acetic anhydride and 90% hydrogen peroxide, the temperature being kept below −5°. Diacetyl peroxide was isolated as the upper layer on pouring the reaction mixture into cold brine.

90% Hydrogen peroxide was used to prepare dibenzoyl peroxide from benzoic anhydride at 0°, ether being used as a mutual solvent; the yields, however, were low (25—30%).

The unsymmetrical peroxides were made by shaking a solution of the appropriate acyl chloride and perbenzoic acid in chloroform with ice-cold aqueous alkali (Wieland and Razuvaiev, *Annalen*, 1930, **480**, 157). Acetyl benzoyl peroxide was prepared by the atmospheric oxidation of a mixture of benzaldehyde and acetic anhydride in the presence of a trace of dibenzoyl peroxide.

The solid peroxides were recrystallised from benzene–alcohol or benzene–light petroleum (b. p. 60—80°), the temperature being kept below 50°. Aliphatic diacyl peroxides with chains containing 8—14 carbon atoms were obtained pure by extracting the crude peroxide with alcohol, containing a little benzene if necessary, at room temperature and crystallising it at −20°. The m. p. s of new peroxides and of those for which definite values have not been established are given below.

Substituted dibenzoyl peroxides

Substituent	M. p.	Substituent	M. p.	Substituent	M. p.
p-Ethyl	58—59°	*p*-Cyano	165°	3 : 5-Dimethyl	118—120°
p-*iso*Propyl	98	*m*-Fluoro	87—88	3 : 4-Dimethoxy	119—120
p-*tert.*-Butyl	142—143	*m*-Iodo	128	2 : 3-Dimethoxy	97
p-*n*-Octyloxy	61	*o*-Methyl	54	3 : 4-Methylenedioxy	131
p-Acetoxy	120—122	*o*-Methoxy	80	2 : 3 : 4 : 5-Tetrachloro	154
p-(Methyl carbonato)	154	*o*-Benzyloxy	102	6-Chloro-3-nitro	146
p-Fluoro	93	*o*-Fluoro	66—67	3 : 5-Dinitro	158
p-Iodo	157	*o*-Bromo	108	*p*-Ethoxy	131—132

Aliphatic diacyl peroxides

Dioctanoyl	23°	Diundec-10-enoyl	23—24°	Di-5-phenylpenta-2 : 4-dienoyl	108—110°
Dilauroyl	41—42	Di(hexa-2 : 4-dienoyl)	113—114	Di-*p*-methoxycinnamoyl	93
Dimyristoyl	59	Bis-β*γ*-dibromobutyryl	76—78	Di-*p*-nitrocinnamoyl	140
Dipalmitoyl	67—68				

Unsymmetrical diacyl peroxides

Benzoyl *m*-nitrobenzoyl	101°	Benzoyl *p*-nitrobenzoyl	113—114°	Adipoyl dibenzoyl	93—94°
Benzoyl stearoyl	78—79			Dibenzoyl phthaloyl	119

Most of the solid peroxides were obtained highly pure and assayed at better than 98% (by the iodometric method). Liquid peroxides were dissolved in the monomer, the peroxide concentration determined in an aliquot portion, and the concentration adjusted subsequently. Solutions of the unstable bisphenylacetyl, dibut-3-enoyl, and bis-*o*-iodobenzoyl peroxides were made up at −20° to avoid serious decomposition.

Monomer Purity, and Determination of Polymerisation Rate.—The styrene was initially of 99·6% purity. It was further purified by washing it with alkaline sodium dithionite (hydrosulphite) and water, drying it, and heating it for 15 minutes at 70—80° with solid potassium hydroxide and sodium. Finally, it was distilled under nitrogen in an all-glass apparatus and had b. p. 83°/100 mm. The pure monomer was stored in the dark at −30°.

The rate of polymerisation was determined dilatometrically. The dilatometers were of 10-ml. capacity, and the volume changes were observed in a precision capillary of 1 mm. bore. They were calibrated directly by precipitating and weighing the polymer formed for an observed contraction. To facilitate cleaning and filling, the dilatometers were in two parts, the junction consisting of a cone and socket. The two parts were firmly held together by springs, and leakage of monomer was prevented by the use of a mercury seal. The rate of polymerisation was adjusted so that the heat of reaction (0·5—1·5 cal./min.) could be dissipated, and adequate temperature control maintained. The thermostat bath was kept at 70° ± 0·05°. The polymerisation was normally taken to about 3%, and over this range the rate of reaction was almost constant. A few peroxides which gave radicals of low reactivity or reacted rapidly with the styrene gave a polymerisation rate which fell off rapidly with time. In these cases the initial slope was determined.

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CHEMICAL RESEARCH DIVISION,
FORT DUNLOP, BIRMINGHAM.

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688. *Syntheses of Polycyclic Systems. Part I. A New Synthesis of Phenanthridine and Phenanthridine Derivatives.*

By E. A. BRAUDE and J. S. FAWCETT.

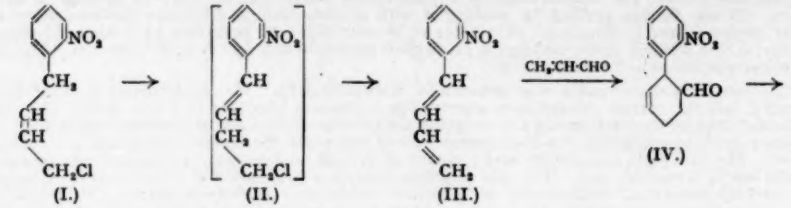
A novel synthesis of phenanthridine and phenanthridine derivatives is described. *o*-Nitrophenylbutadiene (III), prepared by the action of diazotised *o*-nitroaniline on butadiene and treatment of the resulting chlorobutene (I) with alcoholic potassium hydroxide, reacts with acraldehyde to give 2-formyl-1 : 2 : 3 : 4-tetrahydro-2′-nitrodiphenyl (IV). This undergoes catalytic hydrogenation and simultaneous dehydration to give the octahydrophenanthridine (VIII), which on dehydrogenation by selenium affords phenanthridine in an overall yield of 15% based on *o*-nitroaniline.

o-Nitrophenylbutadiene similarly reacts with acrylic acid to give 1 : 2 : 3 : 4-tetrahydro-2′-nitrodiphenyl-2-carboxylic acid (X) and with maleic anhydride to give the adduct (XIV). Reduction of the nitro-group in (X) followed by dehydration affords the tetrahydrophenanthridone (XII), which is dehydrogenated to phenanthridone. The acid (X) and the adduct (XIV) can also be converted directly into phenanthridone by selenium.

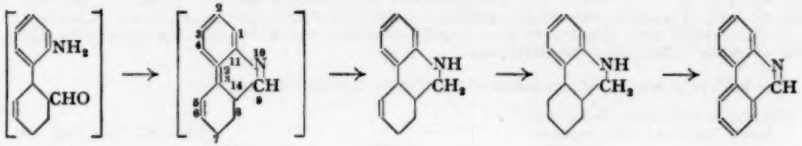
ALTHOUGH a variety of synthetical routes to phenanthridine and its derivatives have been described (for a summary, see Theobald and Schofield, *Chem. Reviews*, 1950, **46**, 171), many of the methods hitherto available are either restricted in scope or involve relatively inaccessible intermediates. Moreover, few of the existing methods are readily adaptable to the synthesis of hydrophenanthridine structures such as occur in certain groups of alkaloids and other natural products. A new synthetical approach is now illustrated with respect to the parent base and some of its simple derivatives. The method resembles some of the earlier ones in that it involves the cyclisation of a diphenyl derivative carrying an unsaturated carbon and nitrogen function, respectively, in the *o*- and the *o*′-position : it differs from earlier methods in the preparation of the diphenyl derivatives and in the choice of the *oo*′-substituents.

The key intermediate in the present synthesis is *o*-nitrophenylbutadiene (III), which is prepared in high yield by the action of *o*-nitrobenzenediazonium chloride on butadiene in the presence of cupric chloride and treatment of the resulting 1-chloro-4-*o*-nitrophenylbut-2-ene (I) with alcoholic potassium hydroxide. Analogous reactions have been carried out with nitrobenzene- and several other diazonium chlorides (Meerwein, Bückner, and Emster, *J. pr. Chem.*,

1939, **152**, 237; Koelsch and Bockelheide, *J. Amer. Chem. Soc.*, 1944, **66**, 412; Bergmann and Schapiro, *J. Org. Chem.*, 1947, **12**, 57; L'Ecuyer, Turcotte, *et al.*, *Canad. J. Res.*, 1947, **25**, 575; 1948, **26**, 70; Rai and Mathur, *J. Indian Chem. Soc.*, 1947, **24**, 383, 413; Coyner and Ropp, *J. Amer. Chem. Soc.*, 1948, **70**, 2283; 1950, **72**, 3960). The initial 1 : 4-addition reaction



(I.) (II.) (III.) (IV.)



(V.) (VI.) (VII.) (VIII.) (IX.)

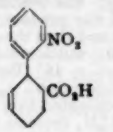
almost certainly takes place by homolytic decomposition of the diazonium salt into aryl radicals and chlorine atoms (cf. Koelsch and Bockelheide, *loc. cit.*). The subsequent dehydrochlorination is probably preceded by a rearrangement of the unconjugated but-2-ene (I) to the conjugated but-1-ene (II), which then undergoes a 1 : 2-elimination reaction. The prototropic change will be catalysed by the alkali and facilitated by the strongly electron-attracting nitro-substituent.

The diene readily undergoes a Diels–Alder reaction with acraldehyde, reaction being substantially complete after 6 hours at 80°. The condensation of phenylbutadiene with acraldehyde requires considerably more drastic conditions (Lehmann and Paasche, *Ber.*, 1935, **68**, 1146; Lehmann, *ibid.*, 1936, **69**, 631), and *o*-tolylbutadiene fails to react (Braude and Fawcett, forthcoming paper), so the Diels–Alder reaction is strongly facilitated by an electron-attracting substituent. The structure of the resulting 2-formyl-1 : 2 : 3 : 4-tetrahydro-2′-nitrodiphenyl (IV), a low-melting solid which was characterised by a semicarbazone and a 2 : 4-dinitrophenylhydrazone, follows from its conversion into phenanthridine (see below). The orientation of the addition reaction corresponds to that observed with the reaction between phenylbutadiene and acraldehyde (Meek, Lorenzi, and Cristol, *J. Amer. Chem. Soc.*, 1949, **71**, 1830) and none of the possible alternative 3-formyl derivative was isolated. The nitro-aldehyde (IV) readily undergoes catalytic hydrogenation in the presence of Raney nickel, and the resulting amino-aldehyde (V) undergoes spontaneous intramolecular dehydration and further hydrogenation, giving 5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-octahydrophenanthridine (VIII) which was prepared by Kruber (*Ber.*, 1939, **72**, 771) by reduction of phenanthridone with sodium and alcohol. Octahydrophenanthridine was characterised as the picrate and the benzoyl derivative. When the catalytic reduction of the nitro-aldehyde (IV) in the presence of Raney nickel was interrupted at an intermediate stage, a hexahydrophenanthridine was obtained which exhibited the ultra-violet light absorption expected for (VII).

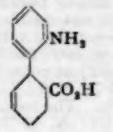
When heated with selenium at 330°, octahydrophenanthridine was converted in good yield into phenanthridine (IX). The overall yield of the five-step synthesis is 15%, based on *o*-nitroaniline. Dehydrogenation of octahydrophenanthridine by selenium at 250° afforded a low yield of a tetrahydrophenanthridine, which was isolated as the picrate and was not identical with the 5 : 6 : 7 : 8-tetrahydro-derivative obtained by Hollingworth and Petrow (*J.*, 1948, 1537; cf. Kenner, Ritchie, and Statham, *J.*, 1937, 1169).

The reaction between *o*-nitrophenylbutadiene and acrylic acid proceeds somewhat less readily than the reaction with acraldehyde, but as in the case of phenylbutadiene (Meek, Lorenzi, and Cristol, *J. Amer. Chem. Soc.*, 1949, **71**, 1830; Ropp and Coyner, *ibid.*, p. 1832; Alder, Vagt, and Vogt, *Annalen*, 1949, **565**, 135) only the product with the desired orientation, in this case 1 : 2 : 3 : 4-tetrahydro-2′-nitrodiphenyl-2-carboxylic acid (X), is obtained. The constitution of the acid, which was isolated in *cis*- and *trans*-forms each characterised by a

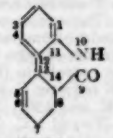
benzylamine salt, is proved by its ultra-violet light absorption properties and by the reactions described below.



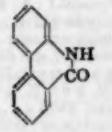
(X.)



(XI.)



(XII.)



(XIII.)

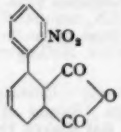
The conversion of the nitro-acid (X) into phenanthridone was effected by three different routes:

(i) Reduction of the nitro-group by catalytic hydrogenation in the presence of Raney nickel afforded the amino-acid (XI). In contrast to 2′-aminodiphenyl-2-carboxylic acid, which undergoes spontaneous dehydration to phenanthridone (Graebe and Wander, *Annalen*, 1893, **276**, 245), the tetrahydro-acid (XI) sublimes unchanged and is not cyclised on treatment with hot potassium hydroxide solution. Dehydrogenation and cyclisation to phenanthridone (XIII) was, however, readily effected by selenium at 250°.

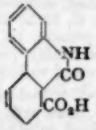
(ii) Reduction of the nitro-acid (X) with boiling alkaline sodium dithionite (hydrosulphite) solution afforded 7 : 8 : 13 : 14-tetrahydrophenanthridone (XII), which was dehydrogenated to phenanthridone by selenium at 250°. It is noteworthy that in this reaction cyclisation occurs under alkaline conditions; since the amino-acid (XI) is unaffected by strong alkali, it must be presumed that cyclisation takes place at an intermediate reduction stage of the nitro-group.

(iii) The nitro-acid (X) can also be converted directly into phenanthridone, though necessarily in lower yield, by heating it with selenium at 250°. Under these conditions, dehydrogenation of the *cyclo*hexenyl group and reduction of the nitro-group take place simultaneously, the acid acting as hydrogen-donor as well as hydrogen-acceptor. Since only 4 atoms of hydrogen per molecule are made available in the dehydrogenation, whereas 6 atoms are required for complete reduction of the nitro-group, the 50% yield of phenanthridone obtained in the reaction represents 75% of the theoretical.

A further route to phenanthridone is provided by the addition of *o*-nitrophenylbutadiene to maleic anhydride to give the adduct (XIV) which is converted into phenanthridone when



(XIV.)



(XV.)

heated with selenium at 250°. The adduct (XIV) is also hydrolysed by hot alkali to the corresponding tetrahydro-dicarboxylic acid, which undergoes simultaneous reduction and cyclisation on treatment with sodium dithionite, giving the tetrahydrophenanthridonecarboxylic acid (XV).

Each of the three components—nitroamine, diene, and dienophile—employed in the present synthesis is readily capable of structural variation, and further applications will be described later.

Experimental.

(M. p.s are uncorrected. Light-absorption data refer to ethanol solutions unless otherwise stated.)

1-Chloro-4-o-nitrophenylbut-2-ene.—*o*-Nitroaniline (140 g.) was warmed with concentrated hydrochloric acid (240 ml.) and water (200 ml.) and then cooled in an ice-bath. Sodium nitrite (70 g.) in water (120 ml.) was slowly added during 1 hour at 0°. This diazotised solution was kept ice-cold while it was gradually added to a stirred mixture of butadiene (120 ml.), acetone (1 l.), sodium acetate solution (80 g. in 100 ml. of water), and cupric chloride solution (30 g. in 50 ml. of water), cooled in ice–salt. The reaction mixture was stirred overnight. The oil which separated was extracted with ether, the extract washed with water and dried, and the ether evaporated, to give the crude *1-chloro-4-o-nitrophenylbut-2-ene* (160 g.), a small quantity of which was purified by fractional distillation, b. p. 126°/5 × 10^{-3} mm., n_D^{20} 1·5653 (Found: N, 6·4. $C_{10}H_{10}O_2NCl$ requires N, 6·6%).

1-o-Nitrophenylbuta-1 : 3-diene.—The crude 1-chloro-4-*o*-nitrophenylbut-2-ene (160 g.) was dissolved in methanol (400 ml.), and a solution of potassium hydroxide (110 g.) in methanol (600 ml.) added to the stirred solution, the temperature being kept between 20° and 30° by occasional cooling. The brown crystalline product was filtered off, washed with water, and, after treatment with charcoal, crystallised from methanol, to give pale yellow needles of *1-o-nitrophenylbuta-1 : 3-diene* (90 g.), m. p. 67° (Found:

C, 68·6; H, 5·4; N, 7·8. $C_{19}H_{19}O_2N$ requires C, 68·6; H, 5·1; N, 8·0%). Light absorption: $\lambda_{max.}$ 2580, 2650, 2810, and 3350 A.; ε = 21,500, 20,500, 17,500, and 4300, respectively.

2-Formyl-1 : 2 : 3 : 4-tetrahydro-2'-nitrodiphenyl.—The above butadiene (24 g.) was refluxed with acraldehyde (12 g.) for 5 hours. The excess of aldehyde was distilled out, and the product distilled under high vacuum. A small amount of unchanged diene (*ca.* 1 g.) sublimed first and then the *diphenyl derivative* (17 g.) distilled as a yellow-orange liquid, b. p. 100° (bath)/10^{-4} mm., which solidified on cooling and crystallised from light petroleum (b. p. 60—80°) as colourless rods, m. p. 46° (Found: C, 67·5; H, 5·6; N, 6·1. $C_{13}H_{13}O_2N$ requires C, 67·5; H, 5·7; N, 6·1%). Light absorption: $\lambda_{max.}$ 2510, 2580, and 2800 A.; ε = 4400, 4500, and 4900, respectively. The *semicarbazone* separated from ethanol as colourless crystals, m. p. 184° (Found: C, 58·5; H, 5·7; N, 19·75. $C_{14}H_{16}O_2N_4$ requires C, 58·3; H, 5·6; N, 19·4%). The *2 : 4-dinitrophenylhydrazone* separated from ethyl acetate in yellow crystals, m. p. 161° (Found: C, 55·2; H, 4·3; N, 17·1. $C_{19}H_{17}O_4N_5$ requires C, 55·5; H, 4·15; N, 17·0%). Light absorption in chloroform: Maximum at 3600 A.; ε = 21,600.

5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-Octahydrophenanthridine.—The foregoing aldehyde (8 g.) in ethanol (300 ml.) was hydrogenated at 20°/1 atm. in the presence of Raney nickel (0·5 g.). After 8 hours, 3·9 mols. of hydrogen had been absorbed. Filtration and evaporation of the solution gave 5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-octahydrophenanthridine (4 g.), which, crystallised from aqueous ethanol, had m. p. 72° (Found: C, 83·5; H, 9·2; N, 7·3. Calc. for $C_{13}H_{17}N$: C, 83·4; H, 9·1; N, 7·5%); Kruber (*Ber.*, 1939, **72**, 771) gives m. p. 74°. Light absorption: $\lambda_{max.}$ 2510, 2560, and 3040 A.; ε = 7800, 7100, and 2200, respectively. The benzoyl derivative crystallised from aqueous methanol as colourless needles, m. p. 142° (Found: C, 82·5; H, 7·4; N, 4·85. Calc. for $C_{20}H_{21}ON$: C, 82·45; H, 7·2; N, 4·8%); Kruber (*loc. cit.*) gives m. p. 140°. The *picrate* crystallised from ethanol as orange-yellow prisms, m. p. 167° (Found: C, 55·0; H, 4·85; N, 13·3. $C_{19}H_{20}O_7N_4$ requires C, 54·8; H, 4·8; N, 13·5%).

7 : 8 : 9 : 10 : 13 : 14-Hexahydrophenanthridine.—The diphenyl-aldehyde (5·5 g.) in ethanol (200 ml.) was hydrogenated at atmospheric pressure in the presence of Raney nickel (0·5 g.). The hydrogenation was stopped after 3 hours when 1·85 l. (3·2 mols.) of hydrogen had been absorbed. Filtration and concentration of the solution gave a pale yellow, viscous oil (4·5 g.). Distillation of the product at 10^{-5} mm. gave a colourless sublimate of *7 : 8 : 9 : 10 : 13 : 14-hexahydrophenanthridine* (2·5 g.), which separated from methanol as crystals, m. p. 104—105° (Found: C, 84·45; H, 8·25; N, 7·4. $C_{13}H_{15}N$ requires C, 84·3; H, 8·1; N, 7·6%). Light absorption: $\lambda_{max.}$ 2510, 2560, and 3040 A.; ε = 6400, 7200, and 2500, respectively.

Phenanthridine and Tetrahydrophenanthridine.—(*a*) 5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-Octahydrophenanthridine (1 g.) was heated with selenium (3 g.) at 250° for ½ hour and then at 330° for 12 hours. On cooling, the residue was extracted with ether. Evaporation of the ether and sublimation of the product gave phenanthridine (0·9 g.), m. p. 105—106°, undepressed on admixture with an authentic specimen, kindly provided by Dr. A. G. Caldwell.

(*b*) 5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-Octahydrophenanthridine (1 g.) was heated with selenium (3 g.) at 250° for 3 hours. Extraction with ether gave a mixture of unchanged octahydrophenanthridine and a tetrahydrophenanthridine, isolated as a *picrate*, which crystallised from ethanol as yellow needles, m. p. 210—212° (Found: C, 55·5; H, 4·0; N, 13·6. $C_{19}H_{18}O_7N_4$ requires C, 55·4; H, 3·9; N, 13·6%). On admixture with the picrate, m. p. 211—213°, prepared from an authentic sample of 5 : 6 : 7 : 8-tetrahydrophenanthridine kindly provided by Dr. V. Petrow (cf. Hollingworth and Petrow, *J.*, 1948, 1537), the m. p. was depressed to 205—207°.

1 : 2 : 3 : 4-Tetrahydro-2'-nitrodiphenyl-2-carboxylic Acid.—(*a*) *o*-Nitrophenylbutadiene (20 g.) and acrylic acid (20 g.) were refluxed together for 18 hours. Excess of acrylic acid was distilled off, and the residue dissolved in ether. The ethereal extract was shaken twice with sodium carbonate solution. Acidification of the carbonate solution gave the (? trans-)*acid* (22 g.), which crystallised from methanol as colourless prisms, m. p. 141° (Found: C, 63·3; H, 5·3; N, 5·9. $C_{13}H_{13}O_4N$ requires C, 63·2; H, 5·3; N, 5·7%). Light absorption: $\lambda_{max.}$ 2510, inflection at 2900 A.; ε = 6700 and 2500, respectively. The *benzylamine* salt crystallised from carbon tetrachloride as fine rods, m. p. 120° (Found: C, 67·4; H, 6·4; N, 7·6. $C_{20}H_{22}O_4N_2$ requires C, 67·8; H, 6·25; N, 7·9%). The acid (m. p. 141°) was recovered unchanged after 4 hours in boiling 0·1% sodium hydroxide solution. It was decomposed when heated with 10% sodium hydroxide solution.

(*b*) In one experiment, *o*-nitrophenylbutadiene (6 g.) and acrylic acid (4 g.) were refluxed together for 12 hours. The mixture was extracted with sodium carbonate solution, which on acidification gave an isomeric (?cis-)*acid* (5·6 g.) which, crystallised from aqueous methanol, had m. p. 122—123° (Found: C, 62·9; H, 5·3; N, 6·1%). Light absorption in ethanol: $\lambda_{max.}$ 2510, 2560, and 2900 A.; ε = 4800, 4800, and 1850, respectively. The *benzylamine* salt crystallised from carbon tetrachloride and had m. p. 125—126°, depressed to 105° on admixture with the isomeric salt obtained as in (*a*) (Found: N, 7·9%).

2'-Amino-1 : 2 : 3 : 4-tetrahydrodiphenyl-2-carboxylic Acid.—The nitro-acid (5·8 g.) in ethanol (200 ml.) was shaken in an atmosphere of hydrogen in the presence of Raney nickel until 1700 ml. (3 mols.) of hydrogen (at 20°/748 mm.) had been absorbed. Filtration and concentration of the solution gave the *amino-acid* (3·5 g.) which crystallised from methanol as rods, m. p. 175—177° (Found: C, 71·5; H, 6·5; N, 6·7. $C_{13}H_{15}O_2N$ requires C, 71·9; H, 6·9; N, 6·45%). Light absorption in *cyclo*hexane: $\lambda_{max.}$ 2510, inflection at 2560 A.; ε = 15,500 and 15,000, respectively. This amino-acid failed to give a picrate and was not cyclised when heated at 200° or refluxed with 10% sodium hydroxide solution.

Phenanthridone and 7 : 8 : 13 : 14-Tetrahydrophenanthridone.—(*a*) The nitro-acid (1 g.) and selenium (2 g.) were heated together at 150° for 1 hour. The temperature was gradually raised to 300°, and heating continued for a further hour. On cooling, the residue and sublimate were ground to a fine powder

and extracted with chloroform (Soxhlet). Evaporation of the solution gave phenanthridone (0·35 g.), which crystallised from ethanol as needles, m. p. 290—293°, undepressed on admixture with an authentic specimen, prepared by Smith's method (*J. Amer. Chem. Soc.*, 1948, **70**, 320).

(*b*) The amino-acid (70 mg.) and selenium (300 mg.) were heated in a sealed tube at 250° for 1 hour and then at 330° for 2 hours. Extraction of the mixture with hot methanol gave phenanthridone as pale yellow needles (30 mg.), m. p. 285°, undepressed on admixture with an authentic specimen.

(*c*) The nitro-acid (1 g.), sodium dithionite (3·5 g.), and 10% sodium hydroxide solution (20 ml.) were refluxed together for 30 minutes. On cooling and acidification with acetic acid, 7 : 8 : 13 : 14-*tetrahydrophenanthridone* (0·5 g.) was obtained, which crystallised from methanol as needles, m. p. 194—195° (Found : C, 78·3; H, 6·6; N, 6·7. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6; N, 7·0%). Light absorption : $\lambda_{max.}$ 2510 and 2560 A., ϵ = 9800 and 9100, respectively.

7 : 8 : 13 : 14-Tetrahydrophenanthridone (1 g.) and selenium (1 g.) were heated together at 250° for 1 hour. Extraction of the mixture with hot methanol gave phenanthridone (0·4 g.), m. p. 288°, undepressed on admixture with an authentic specimen.

1 : 2 : 3 : 4-*Tetrahydro-2′-nitrodiphenyl-2* : 3-*dicarboxylic Anhydride and Acid.*—1-*o*-Nitrophenylbutadiene (4 g.), maleic anhydride (2·5 g.), and benzene (5 ml.) were refluxed together for 15 minutes. On cooling, the above *anhydride* (6 g.) separated, and crystallised from ethyl acetate as prisms, m. p. 154° (Found : C, 61·4; H, 4·1; N, 5·1. $C_{14}H_{11}O_5N$ requires C, 61·5; H, 4·05; N, 5·1%). Light absorption in chloroform : $\lambda_{max.}$ 2570, 2650, and 2800 A., inflection 2500 A. ; ϵ = 5700, 5300, 4100, and 4900, respectively. The anhydride (0·5 g.) was dissolved in hot 10% sodium hydroxide solution (20 ml.); acidification of the solution gave the *acid* (0·48 g.), which crystallised from methanol as colourless prisms, m. p. 215° (Found : C, 57·8; H, 4·6; N, 5·2. $C_{14}H_{13}O_6N$ requires C, 57·7; H, 4·5; N, 4·8%).

When the anhydride (1 g.) was heated with selenium (3 g.) at 200° for 2 hours and then at 250° for 1 hour, phenanthridone (0·3 g.) was obtained as a white sublimate, m. p. 285°, undepressed on admixture with an authentic specimen.

Reduction of the Foregoing Anhydride by Sodium Dithionite.—The above anhydride (2 g.) and sodium dithionite (7 g.) were dissolved in 10% aqueous sodium hydroxide (40 ml.). The solution was refluxed for 30 minutes and then neutralised by addition of acetic acid. On cooling, the product separated in fine colourless needles (0·95 g.). It could not be crystallised, but was purified by precipitation with acid from alkaline solution, and had m. p. 216° (Found : C, 68·5; H, 5·6; N, 5·6. $C_{14}H_{13}O_6N$ requires C, 69·15; H, 5·4; N, 5·75%). Light absorption : $\lambda_{max.}$ 2510, inflection at 2560 A. ; ϵ = 11,400 and 11,000, respectively. The product dissolved in sodium carbonate solution with slow evolution of carbon dioxide. It was not diazotised by sodium nitrite solution and is formulated as 7 : 8 : 13 : 14-*tetrahydrophenanthridone*-8-*carboxylic acid.*

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
SOUTH KENSINGTON, LONDON, S.W.7.

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689. *Syntheses of Polycyclic Systems. Part II.** 8-*Ketodibenzo*[c,mn]-*acridine and* 8 : 16-*Diazadibenzo*[b,k]*perylene.*

By E. A. BRAUDE and J. S. FAWCETT.

The Diels–Alder reaction between *o*-nitrophenylbutadiene and 1 : 4-naphthaquinone is accompanied by dehydrogenation of the resulting tetrahydro-1-*o*-nitrophenylanthraquinone (I) to the dihydroanthraquinone (II) or the anthraquinone (III), depending on the conditions employed. On treatment with methanolic potassium hydroxide, the tetrahydroanthraquinone (I) undergoes an internal oxidation–reduction reaction and simultaneous dehydration to the anthrone (V), which is also obtained by reduction of the anthraquinone (III) with sodium dithionite (hydrosulphite).

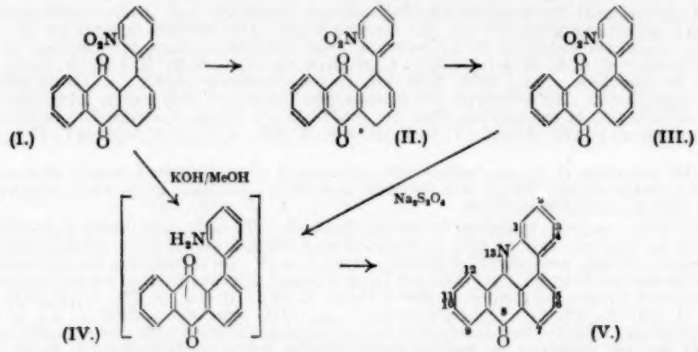
The addition of *o*-nitrophenylbutadiene to 1 : 4-benzoquinone in nitrobenzene solution gives a mixture of 1 : 5-di-*o*-nitrophenylanthraquinone (VI) and the 1 : 8-isomer (VIII). The former undergoes reduction and dehydration to 8 : 16-diazadibenzo[*b*,*k*]perylene (VII); the latter undergoes reduction and cyclisation to (IX).

THE work described in this paper illustrates the extension of the new phenanthridine synthesis described in Part I (preceding paper) to higher polycyclic derivatives.

o-Nitrophenylbutadiene readily reacts with 1 : 4-naphthaquinone in boiling benzene to give a mixture of the expected tetrahydro-1-*o*-nitrophenylanthraquinone (I) and the corresponding

* Part I, preceding paper.

dihydroanthraquinone (II). The position of the two non-aromatic hydrogen atoms in (II) has not been proved, but is not in doubt since 1 : 4-dihydroquinones are invariably the first oxidation products of tetrahydro-anthra- or -naphtha-quinones (Diels and Alder, *Ber.*, 1929, **62**, 2337; Fieser, *J. Amer. Chem. Soc.*, 1948, **70**, 3165). Partial dehydrogenation accompanying Diels–Alder reactions has previously been observed in a number of cases, though usually under rather more drastic reaction conditions (cf. Clar, *Ber.*, 1936, **69**, 1686; Bergmann *et al.*, *J. Amer. Chem. Soc.*, 1938, **60**, 1331; 1942, **64**, 176; *J. Org. Chem.*, 1942, **7**, 303; Swain and Todd, *J.*, 1942, 626). The formation of the dihydroanthraquinone (II) under relatively mild conditions shows that the dehydrogenation is facilitated by the strongly electron-attracting *o*-nitrophenyl substituent; this effect is, of course, analogous to the enhanced reactivity of the methyl group in nitrotoluene as compared with toluene towards oxidising agents.



When the unpurified tetrahydroanthraquinone (I) is treated with warm 2% methanolic potassium hydroxide solution, a rapid colour change takes place and the desired cyclisation product (V) is obtained in 65% yield. The direct conversion of (I) into (V) under these conditions is somewhat unexpected and presumably proceeds through 1-*o*-aminophenylanthraquinone (IV) which then undergoes spontaneous dehydration. Since 1-*o*-nitrophenylanthraquinone remains unchanged even in boiling methanolic potassium hydroxide (see below), the direct conversion of (I) into (V) must involve a hydrogen-transfer reaction in which the tetrahydroanthraquinone grouping is dehydrogenated, probably intramolecularly, by the *o*-nitro-substituent. A similar internal oxidation–reduction reaction, though under very much more drastic conditions, occurs in the conversion of 1 : 4 : 5 : 6-tetrahydro-2-*o*-nitrophenylbenzoic acid into phenanthridone when heated with selenium (Part I, *loc. cit.*).

When the condensation between *o*-nitrophenylbutadiene and naphthaquinone was carried out in nitrobenzene at 100° the main product isolated was the dihydroanthraquinone (II), and at 150° the only product obtained was 1-*o*-nitrophenyl-9 : 10-anthraquinone (III). Here, dehydrogenation is evidently effected intermolecularly, with the nitrobenzene solvent acting as oxidising agent (cf. Bergmann *et al.*, *loc. cit.*; Swain and Todd, *loc. cit.*). The dihydroanthraquinone (II) is oxidised to the anthraquinone (III) when warmed with methanolic potassium hydroxide. The fully oxidised anthraquinone (III) remains unchanged even in boiling methanolic potassium hydroxide, but undergoes simultaneous reduction and dehydration to the anthrone (V) on treatment with alkaline sodium dithionite, presumably *via* the aminoquinone (IV). 8-Ketodibenzo[*c*, *mn*]acridine (Ring Index 3307) has been synthesised by Koelsch (*J. Amer. Chem. Soc.*, 1936, **58**, 1325) by another route starting from *o*-aminodiphenyl. It does not form a picrate or 2 : 4-dinitrophenylhydrazone under the usual conditions. When warmed with zinc and hydrochloric acid, it is reduced to a dark blue dihydro-derivative, which is readily oxidised back to the anthrone on exposure to air.

The ultra-violet light absorption of (V) closely resembles that of the carbocyclic analogue (Fig. 1), in accordance with the general experience that the replacement of one C:C by a C:N group in cyclic systems does not appreciably alter the spectral characteristics in this region (cf. Braude, *Ann. Reports*, 1945, **42**, 108; Barany, Braude, and Pianka, *J.*, 1949, 1898; Albert, Brown, and Cheeseman, *J.*, 1951, 474; Clemo and Felton, *ibid.*, p. 671).

The reaction between *o*-nitrophenylbutadiene and benzoquinone in benzene or nitrobenzene

gives partly dehydrogenated mono- and di-addition products which are difficult to separate. However, when the diene (2 moles) and benzoquinone (1 mole) are heated together in nitrobenzene at 100° for 12 hours, the fully dehydrogenated di-addition product, 1 : 5-bis-*o*-nitrophenylanthraquinone (VI) can be isolated in 20% yield, together with a smaller quantity of the 1 : 8-isomer (VIII). The structures of the two products follow from the cyclisation reactions described below. The formation of both possible di-adducts in the reaction between benzoquinone and unsymmetrically substituted dienes has been observed in other cases (cf. Diels and Alder, *Ber.*, 1929, **62**, 2337), but with phenylbutadiene only the 1 : 5-di-adduct appears to be formed (Bergmann *et al.*, *J.*, 1939, 391; *J. Org. Chem.*, 1942, **7**, 303).

On treatment with sodium dithionite in boiling aqueous ethanol, the anthraquinone (VI) is converted directly into the desired fully cyclised product (VII), whereas the anthraquinone (VIII) is converted into the anthrone (IX), which forms a picrate and exhibits ultra-violet light absorption properties very similar to those of the parent (V).

FIG. 1.

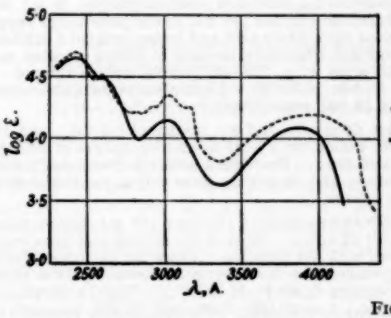


FIG. 2.

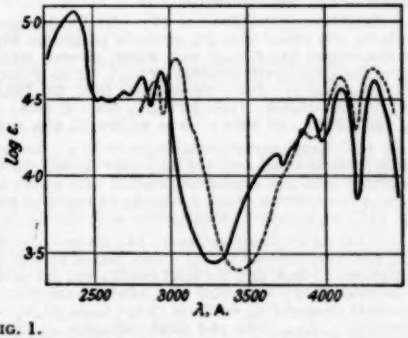


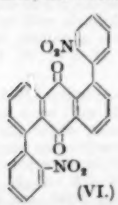
FIG. 1.

Light absorption of (V) (———) *and its carbocyclic analogue* (– – – –) *in chloroform.*

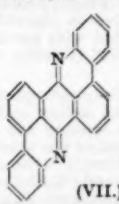
FIG. 2.

Light absorption of (VII) (———) *in dioxan and its carbocyclic analogue* (– – – –; *from Clar*, loc. cit.) *in benzene.*

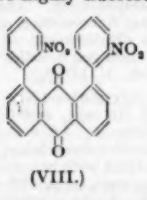
The heptacyclic compound (VII) is a light yellow solid which is almost insoluble in the usual solvents and does not melt below 360°, and is characterised by a picrate. Its light-absorption properties (Fig. 2) closely resemble those of the carbocyclic analogue (Clar, *Ber.*, 1932, **65**, 846; Zinke and Ziegler, *Ber.*, 1940, **73**, 115; Schauenstein and Bürgermeister, *Ber.*, 1943, **76**, 205) and, as would be expected, its solutions are highly fluorescent. An examination of some



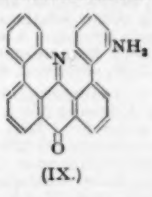
(VI.)



(VII.)



(VIII.)



(IX.)

possible biological properties was kindly carried out by Professor A. Haddow, who reports that, at a dosage of 250 mg./kg., it appeared to be without effect on the growth of the Walker rat carcinoma 256.

EXPERIMENTAL.

(M.p.s are uncorrected.)

Reaction between 1-*o*-*Nitrophenylbutadiene and Naphthaquinone.*—(*a*) 1-*o*-Nitrophenylbutadiene (12 g.) (Part I, *loc. cit.*), naphthaquinone (8 g.), and benzene (50 ml.) were refluxed for 24 hours. Most of the solvent was removed by distillation and the residue (14 g.) solidified; it was a mixture of 1 : 4 : 11 : 12-tetrahydro- and 1 : 4-*dihydro*-1-*o*-*nitrophenylanthra*-9 : 10-*quinone*, from which the latter was

isolated by crystallisation from ethyl acetate as yellow crystals, m. p. 188—190° (Found: C, 72·3; H, 4·0. $C_{20}H_{13}O_4N$ requires C, 72·5; H, 3·95%).

A suspension of the dihydro-compound (0·35 g.) in 2% methanolic potassium hydroxide solution (20 ml.) was boiled in a stream of oxygen for 30 minutes, and the mixture was cooled, diluted with water, and filtered, to give 1-*o*-*nitrophenylanthraquinone* (0·28 g.), which crystallised from ethyl acetate in yellow prisms, m. p. 213° (Found: C, 72·9; H, 3·3; N, 4·2. $C_{20}H_{11}O_4N$ requires C, 72·9; H, 3·4; N, 4·2%). Light absorption in chloroform: $\lambda_{max.}$ 2570 and 3380 A.; ε = 44,600 and 2300, respectively.

(*b*) 1-*o*-Nitrophenylbutadiene (2 g.), naphthaquinone (2 g.), and nitrobenzene (10 ml.) were heated together at 100° for 3 hours. On cooling and dilution with ethanol (50 ml.), a pale yellow solid separated (1·7 g.), which was crystallised from ethyl acetate to give 1 : 4-dihydro-1-*o*-nitrophenylanthraquinone, m. p. 186°, undepressed on admixture with the above sample.

(*c*) 1-*o*-Nitrophenylbutadiene (2 g.), naphthaquinone (2 g.), and nitrobenzene (10 ml.) were heated together at 150° for 2 hours. On cooling and dilution with ethanol, a yellow product separated, which crystallised from ethyl acetate to give yellow prisms of 1-*o*-nitrophenylanthraquinone (1·4 g.), m. p. 213°, undepressed on admixture with the sample obtained above.

A suspension of 1-*o*-nitrophenylanthraquinone (0·55 g.) in 10% methanolic potassium hydroxide (40 ml.) was boiled for 30 minutes. On working up the product, unchanged 1-*o*-nitrophenylanthraquinone (0·5 g.) was obtained.

8-*Ketodibenzo*[c,mn]*acridine* (V).—(*a*) Crude tetrahydro-1-*o*-nitrophenylanthraquinone (4 g.) from (*a*) above, was boiled with 2% alcoholic potassium hydroxide solution (50 ml.) in the presence of oxygen. The suspension was diluted with water, filtered, washed with dilute acid and water, and then sublimed, to give the pentacyclic product (2·5 g.), which crystallised from ethyl acetate in yellow needles, m. p. 218°. Koelsch (*J. Amer. Chem. Soc.*, 1936, **58**, 1325) gives m. p. 221—223° from xylene (Found: C, 85·1; H, 3·9; N, 5·0. Calc. for $C_{20}H_{11}ON$: C, 85·4; H, 3·9; N, 5·0%). Light absorption in chloroform: $\lambda_{max.}$ 2420, 3030, and 3860 A.; ε = 42,000, 14,400, and 13,200, respectively.

(*b*) 1-*o*-Nitrophenylanthraquinone (0·75 g.), sodium dithionite (1·5 g.), methanol (15 ml.), and 10% sodium hydroxide solution (15 ml.) were heated under reflux for 1 hour in an atmosphere of nitrogen. The brown solid was filtered off, washed with water, and dried. On boiling with ethyl acetate (150 ml.) it gave a red solution which gradually changed to yellow, and on cooling gave yellow needles (0·45 g.), m. p. 218°, undepressed on admixture with the above material.

1 : 5-*Bis*-o-*nitrophenylanthra*-9 : 10-*quinone*.—1-*o*-Nitrophenylbuta-1 : 3-diene (32 g.), benzoquinone (8 g.), and nitrobenzene (30 ml.) were heated at 100° for 12 hours. Most of the solvent was removed by distillation at 2 mm. and the solid residue was extracted with hot pyridine. From the pyridine solution, the *quinone* (9 g.) separated and after repeated crystallisation from pyridine formed yellow plates, m. p. 311° (Found: C, 69·2; H, 3·1. $C_{26}H_{14}O_6N_2$ requires C, 69·3; H, 3·15%). Light absorption in chloroform: $\lambda_{max.}$ 2580 and 3300, inflection at 2510 A.; ε = 47,000, 7000, and 40,500, respectively. The pyridine-insoluble fraction (0·9 g.) was 1 : 8-*bis*-o-*nitrophenylanthraquinone*, which crystallised from nitrobenzene in yellow rods, m. p. 320° (decomp.) (Found: C, 69·1; H, 3·4; N, 6·1. $C_{26}H_{14}O_6N_2$ requires C, 69·3; H, 3·15; N, 6·2%). Light absorption in chloroform: $\lambda_{max.}$ 2580 and 3150 A.; inflection at 3300 A.; ε = 46,00, 8000, and 6300, respectively. Both products remained unchanged on treatment with hot 10% alcoholic potassium hydroxide solution.

8 : 16-*Diazadibenzo*[b,k]*perylene*.—1 : 5-Bis-*o*-nitrophenylanthraquinone (3 g.), sodium dithionite (10 g.), methanol (30 ml.), and 5% sodium hydroxide solution (60 ml.) were heated under reflux for 1 hour in an atmosphere of nitrogen. The dark green product (2·8 g.) was filtered off, washed with dilute acid and water, boiled with pyridine (10 ml.), filtered, and crystallised from nitrobenzene, to give orange-yellow needles of 8 : 16-*diazadibenzo*[b,k]*perylene*, cf. Ring Index 3833), m. p. >360° (Found: C, 87·8; H, 4·15; N, 7·8. $C_{24}H_{14}N_2$ requires C, 88·1; H, 3·95; N, 7·9%). Light absorption in dioxan: $\lambda_{max.}$ 2380, 2570, 2700, 2810, 2940, 3700, 3920, 4120, and 4350 A.; ε = 117,000, 31,800, 34,000, 40,500, 47,700, 13,200, 20,500, 37,000, and 40,500, respectively. The product is slightly soluble in chloroform and dioxan, forming yellow solutions with a blue fluorescence, and dissolves in concentrated sulphuric acid to give an orange solution. A solution in nitrobenzene when warmed with picric acid gave a *picrate*, which crystallised from nitrobenzene in fine red needles, m. p. 311° (Found: C, 66·2; H, 3·0; N, 11·65. $C_{32}H_{17}O_7N_5$ requires C, 65·9; H, 2·9; N, 12·0%).

12-o-*Aminophenyl*-8-*ketodibenzo*[c,mn]*acridine*.—1 : 8-Bis-*o*-nitrophenylanthraquinone (0·6 g.), sodium dithionite (3 g.), methanol (10 ml.), and 5% aqueous sodium hydroxide (20 ml.) were heated under reflux for 1 hour under nitrogen. After cooling, the solution was diluted with water (20 ml.) and the precipitated 12-o-*aminophenyl*-8-*ketodibenzo*[c,mn]*acridine* was filtered off, dissolved in benzene, chromatographed on an alumina column with benzene–chloroform (1 : 1) as eluent, and finally crystallised from chloroform–methanol as orange rods, m. p. 273—275° (Found: C, 83·4; H, 4·4; N, 7·5. $C_{26}H_{16}ON_2$ requires C, 83·4; H, 4·3; N, 7·5%). Light absorption in chloroform: $\lambda_{max.}$ 2450, 2940, 3030, and 3860, inflection 3200 A.; ε = 48,700, 14,400, 16,500, 13,100, and 7700, respectively. A solution of the anthrone and picric acid in benzene, after warming, deposited the *picrate*, which crystallised from ethyl acetate in orange-yellow prisms, m. p. 253° (decomp.) (Found: C, 64·8; H, 3·45; N, 12·0. $C_{32}H_{19}O_9N_5$ requires C, 64·0; H, 3·2; N, 16·65%).

1 : 4-*Naphthaquinone*.—The direct oxidation of naphthalene has been found a more convenient method for the preparation of this quinone than the conventional method starting from α-naphthol (Conant and Fieser, *J. Amer. Chem. Soc.*, 1924, **46**, 1862; Fieser and Fieser, *ibid.*, 1935, **57**, 491; Fieser, *Org. Synth.*, Coll. Vol. I, 1946, p. 383). The following procedure is adapted from Miller (*J. Russ. Phys. Chem. Soc.*, 1884, **16**, 414; cf. Japp and Miller, *J.*, 1881, **39**, 220). A solution of naphthalene (64 g.) in acetic acid (600 ml.) is gradually added to a well-stirred solution of chromium trioxide (150 g.) in acetic acid (120 ml.) and water (30 ml.) in a 2-l. flask surrounded by ice–salt. The temperature of the

mixture must not be allowed to rise above 0°. Stirring is continued overnight, during which time the reaction mixture gradually attains room temperature; it is essential to use a large volume of freezing-mixture and to replenish it in the evening. The dark green solution is then set aside for 3 days and occasionally stirred. Then the solution is poured into ice-cold water (6 l.) and the yellow precipitate is filtered off, washed with water (200 ml.), and dried in a desiccator. The product is crystallised once from light petroleum (b. p. 80—100°; 500 ml.), giving long yellow needles of 1 : 4-naphthaquinone (25—28 g., 32—35%), m. p. 124—125°.

Light-absorption Measurements.—These were carried out by the photographic method, a Hilger instrument being used (cf. Braude, *J.*, 1945, 490). The curve for the dibenzophenanthrene (Fig. 1) was determined on a sample, m. p. 232°, obtained by an unambiguous synthesis (Braude and Fawcett, forthcoming paper) and identical by mixed m. p. with the product prepared and kindly provided by Dr. E. Clar, but differs somewhat from the curve previously recorded (*Ber.*, 1943, **76**, 609).

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
SOUTH KENSINGTON, LONDON, S.W.7.

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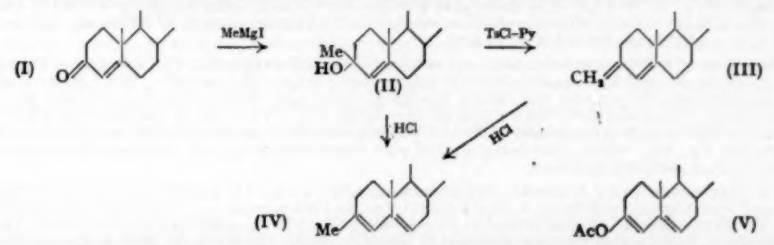
690. *Some Grignard Reactions with Cholest-4-en-3-one.*

By O. C. MUSGRAVE.

The reaction between cholest-4-en-3-one and methylmagnesium iodide gives 3-methylcholest-4-en-3-ol. In the presence of cuprous chloride 3-methylenecholest-4-ene and 3-methylcholesta-3 : 5-diene are also formed; 1 : 4-addition to the αβ-unsaturated carbonyl system is not observed.

THE interaction of cholest-4-en-3-one (I) and methylmagnesium iodide has been found to give an αβ-unsaturated tertiary alcohol, $C_{28}H_{48}O$, which appears to be the product of normal addition to the carbonyl group. The alcohol is considered to be a molecular compound (II) of 3α-methylcholest-4-en-3β-ol and 3β-methylcholest-4-en-3α-ol, by analogy with the related compound (which it resembles closely in optical rotation; see table) formed by the epimeric cholest-4-en-3-ols obtained by the reduction of cholest-4-en-3-one with aluminium *iso*propoxide or lithium aluminium hydride (Schoenheimer and Evans, *J. Biol. Chem.*, 1936, **114**, 567; McKennis and Gaffney, *ibid.*, 1948, **175**, 217). The resolution of the 3-methylcholest-4-en-3-ol molecular compound was however not achieved. Although about half the material was precipitated by digitonin, the attempted isolation of the epimers according to McKennis and Gaffney's method (*loc. cit.*) failed to give pure materials. Thus treatment of the insoluble digitonide with pyridine resulted in dehydration to a diene, as shown by the brown colour developed with tetranitromethane, and crystallisation of the unprecipitated material did not afford a homogeneous specimen.

Treatment of 3-methylcholest-4-en-3-ol with toluene-*p*-sulphonyl chloride and pyridine (cf. Bann, Heilbron, and Spring, *J.*, 1936, 1274) afforded 3-methylenecholest-4-ene (III);



ozonolysis of this compound gave a low yield (6%) of formaldehyde (isolated as the dimedone derivative). Under more vigorous conditions (heating under reflux with alcoholic hydrochloric acid) isomerisation accompanied the dehydration, and 3-methylcholesta-3 : 5-diene (IV) resulted, the m. p. and molecular rotation of which are similar to those of cholesta-3 : 5-diene (see table). Further support for structure (IV) is forthcoming from the optical-rotation dispersion curve

	M. p.	$[M]_D$.	$\lambda_{max.}$ (Å).	ε.
3-Methylcholest-4-en-3-ol molecular compound	115·5°	+304°	—	—
Cholest-4-en-3-ol molecular compound *	141	+324	—	—
3-Methylcholesta-3 : 5-diene	79·5	−493	2390	22,700
Cholesta-3 : 5-diene *	79	−453	2350	23,000

* Schoenheimer and Evans (*loc. cit.*).

which is similar to that of the enol-acetate of cholest-4-en-3-one (V) which also contains a $C_{(5)}$-substituted 3 : 5-diene system. The ready isomerisation of 3-methylenecholest-4-ene on treatment with hydrochloric acid is in agreement with Barton and Brooks's observations (*J.*, 1951, 268) concerning the stability of conjugated diene systems. Although the ultra-violet absorption spectra of these dienes are not entirely identical, both show maximum absorption at $\lambda = 2390$ Å, the value calculated by Woodward's method (Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold, New York, 1949, 185).

Kharasch (*J. Amer. Chem. Soc.*, 1941, **63**, 2308) found that the course of the reaction between methylmagnesium iodide and $\alpha\beta$-unsaturated ketones may be altered from 1 : 2- to 1 : 4-addition by catalytic amounts of cuprous chloride. When cuprous chloride was added to the Grignard reaction with cholest-4-en-3-one, considerable dehydration of the tertiary alcohol occurred with the formation of a mixture of the two dienes, which was partially separated by crystallisation.

Experimental.

3-Methylcholest-4-en-3-ol.—The Grignard reagent prepared from magnesium (0·81 g.), methyl iodide (4·7 g.), and dry ether (20 ml.) was cooled to 0° and a solution of cholest-4-en-3-one (10·6 g.) in dry ether (70 ml.) and dry benzene (5 ml.) was added during 30 minutes. The mixture was heated under reflux for 15 minutes, set aside for 30 minutes, and poured on crushed ice (80 g.) and ammonium chloride (8 g.). The ethereal extract was dried (Na_2SO_4) and evaporated. The residue on crystallisation from acetone–methanol gave *3-methylcholest-4-en-3-ol* (7·73 g.) as needles, m. p. 114—115·5°, $[\alpha]_D^{19}$ +76° (*c*, 1 in benzene) [Found: (i) on a specimen dried at 56°/0·1 mm. for 1 hour: C, 82·3; H, 11·9. $C_{28}H_{48}O,\frac{1}{4}MeOH$ requires C, 82·1; H, 12·1%; (ii) on a specimen dried at 56°/0·1 mm. for 18 hours: C, 83·6; H, 12·1; active hydrogen, 0·26. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1; Active hydrogen, 0·25%]. The compound gave a pale yellow colour with tetranitromethane in chloroform, and a strong Rosenheim reaction.

The residual mother-liquors from the crystallisation afforded, on evaporation, cholest-4-en-3-one, m. p. 78—80°.

3-Methylcholesta-3 : 5-diene.—3-Methylcholest-4-en-3-ol (0·6 g.) was heated under reflux for 2 hours with N/30-ethanolic hydrochloric acid (50 ml.). After removal of the solvent the residual *3-methylcholesta-3 : 5-diene* crystallised from methanol–acetone in laths, m. p. 79—79·5°, $[\alpha]_D^{19}$ −129° (*c*, 1 in chloroform). The diene gave a yellow-brown colour with tetranitromethane in chloroform, which faded rapidly when the solution was kept. Light absorption in *cyclo*hexane: Maxima at 2390 Å ($\varepsilon = 22{,}700$) and 2310 Å ($\varepsilon = 21{,}500$) (Found: C, 87·2; H, 12·2. $C_{28}H_{46}$ requires C, 87·9; H, 12·1%). This diene was also formed when 3-methylenecholest-4-ene was heated under reflux with ethanolic hydrochloric acid.

3-Methylenecholest-4-ene.—3-Methylcholest-4-en-3-ol (0·5 g.) was heated on the water-bath for 15 minutes with toluene-*p*-sulphonyl chloride (0·6 g.) and dry pyridine (5 ml.). The mixture was poured into N/2-hydrochloric acid, and the ether extract was washed successively with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated. A solution of the residue in light petroleum (60—80°; 40 ml.) was filtered through a column of alumina (Brockmann Grade II; 1 × 10 cm.). The filtrate on evaporation afforded *3-methylenecholest-4-ene* (0·45 g.) which crystallised from acetone–methanol in laths, m. p. 63—64°, $[\alpha]_D^{19}$ +50·5° (*c*, 1 in benzene) (Found: C, 87·6; H, 12·2. $C_{28}H_{46}$ requires C, 87·9; H, 12·1%). The diene gave a yellow-brown colour with tetranitromethane in chloroform which faded rapidly when the solution was kept. Light absorption in *cyclo*hexane: Maxima at 2390 Å ($\varepsilon = 17{,}260$) and 2330 Å ($\varepsilon = 16{,}230$).

Ozonolysis of 3-Methylenecholest-4-ene.—A stream of ozonised oxygen (*ca.* 4%) was passed through a solution of the diene (0·9 g.) in chloroform (20 ml.) until absorption was complete. After removal of the solvent under reduced pressure, the residue was boiled with water (20 ml.), acetic acid (5 ml.), and zinc dust (1 g.) for ½ hour and then distilled into an ice-cold receiver. The aqueous distillate was added to a solution of dimedone (1 g.) in ethanol (15 ml.). After a while formaldehyde dimedone separated in long needles (43 mg., 6%) which, after being washed with water, had m. p. 186—188° and did not depress the m. p. of an authentic specimen.

The Catalysed Grignard Reaction.—Dry cuprous chloride (0·3 g.) was added to the Grignard reagent prepared from magnesium (0·24 g.), methyl iodide (1·6 g.), and dry ether (5 ml.). After this had been stirred at 0° for 30 minutes, a solution of cholest-4-en-3-one (2·56 g.) in dry ether (15 ml.) was added during 30 minutes. The reaction mixture was worked up as described above. A solution of the product in acetone–methanol slowly deposited crystals of 3-methylcholest-4-en-3-ol (0·21 g.). Careful concentration of the mother-liquors and addition of methanol resulted in the separation of crude 3-methylcholesta-3 : 5-diene {1·05 g., $[\alpha]_D^{19}$ −111·6° (*c*, 1 in chloroform)}, m. p. 77—78° after repeated crystallisation from acetone–methanol. Light absorption in *cyclo*hexane: Maxima at 2390 Å ($\varepsilon = 21{,}150$) and 2310 Å ($\varepsilon = 19{,}750$) (Found: C, 87·2; H, 12·2. Calc. for $C_{28}H_{46}$: C, 87·9; H, 12·1%). The optical rotation indicates the presence of 91% of 3-methylcholesta-3 : 5-diene and 9% of 3-methylenecholest-4-ene. The pure diene was obtained by heating the crude material with ethanolic hydrochloric acid whereupon the contaminant, 3-methylenecholest-4-ene, underwent isomerisation.

Evaporation of the remaining mother-liquors gave an oil which was dissolved in light petroleum (60—80°; 50 ml.) and filtered through a column of alumina (Brockmann Grade II; 2 × 20 cm.) which was washed with light petroleum (60—80°; 200 ml.) followed by benzene–methanol (49 : 1; 200 ml.). The light petroleum filtrate on evaporation afforded a solid which could not be obtained crystalline. This was purified by dissolving it in light petroleum (40—60°) and filtering it through a column of

alumina (1 × 35 cm.). From the first fractions of the eluate, crude 3-methylenecholest-4-ene [260 mg.; m. p. 60—62°, $[\alpha]_D^{18}$ −28·9° (*c*, 1 in chloroform)] was obtained. The m. p. and optical rotation were unchanged by further chromatographic treatment (Found: C, 87·9; H, 12·1. Calc. for $C_{28}H_{46}$: C, 87·9; H, 12·1%). The optical rotation indicates the presence of 55% of 3-methylenecholest-4-ene and 45% of 3-methylcholesta-3 : 5-diene. Light absorption in *cyclo*hexane: Maxima at 2390 Å (ε = 19,150) and 2330 Å (ε = 18,500). The mixed m. p. with an authentic specimen of 3-methylenecholest-4-ene was 60—64°.

The benzene–methanol filtrate afforded cholest-4-en-3-one (0·9 g.; m. p. 76—78°).

The author thanks Professor F. S. Spring for his interest and Mr. J. Fraser, B.Sc., for experimental assistance.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, May 24th*, 1951.]

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691. *The Cation Exchange Separation of Zirconium and Hafnium.*

By B. A. J. LISTER.

An investigation has been made of the possibility of separating zirconium and hafnium by elution from a cation-exchange column with sulphuric, hydrochloric, nitric, perchloric, and oxalic acids. A method has been developed depending on sulphuric acid elution whereby gram quantities of the two elements, in their naturally occurring proportions, can be separated by one passage through the column. The method is believed to be the simplest and most satisfactory at present available for the separation of zirconium and hafnium on a laboratory scale.

DURING the last two years several papers have appeared dealing with the separation of zirconium and hafnium by ion-exchange methods. Street and Seaborg (*J. Amer. Chem. Soc.*, 1948, **70**, 4268) showed that separation on a cation column was possible, and details of a run with 6N-hydrochloric acid as eluant were published. This was followed by two papers dealing with separation by anion exchange. Kraus and Moore (*ibid.*, 1949, **71**, 3263), using a column of Dowex 1, obtained some separation of tracer concentrations of zirconium and 0·2 mg. of hafnium by elution with a mixture of 0·5M-hydrofluoric acid and 1·0M-hydrochloric acid. Huffman and Lilly (*ibid.*, p. 4147) absorbed the ions on Amberlite IRA—400 from dilute hydrofluoric acid solution and then slowly eluted the fluoro-salts with 0·2M- and 0·01M-hydrochloric acid. By all these three methods the hafnium is eluted first from the column. However, from the point of view of an economic purification of zirconium, it is very much more favourable to elute the large quantity of zirconium and retain on the column the very much smaller hafnium impurity. Such a method has been developed by Hansen *et al.* (*ibid.*, 1950, **72**, 5043), who found that silica gel absorbs hafnium with strong preference from a dry methanol solution of the tetrachlorides. For the present work it was decided to start with the two elements in their naturally occurring proportions and to make use of the differences in the solution complexes of zirconium and hafnium in acid solutions combined with cation exchange to attempt to effect a removal of the small hafnium impurity.

EXPERIMENTAL.

Materials.—Zirconium oxide. "Specpure" oxide from Johnson Matthey Ltd. was used in which no purification from hafnium had been made. Analysis of the hafnium content by optical spectrographic methods and by radiochemical absorption analysis showed 1·5—2% of HfO_2.

Zirconium oxychloride. This was prepared from "Specpure" oxide by dissolution in a mixture of sulphuric and hydrofluoric acids, evaporation to dryness, dissolution of the sulphate in hydrochloric acid, precipitation of the hydroxide with ammonia solution, and redissolution in and crystallisation from hydrochloric acid.

Zirconium nitrate. Samples from different commercial sources showed very wide differences in ease of solubility, although spectrographic analysis for trace impurities and gravimetric analysis for zirconium and nitrate showed them to be very similar. [Analysis of a sample from Hopkin and Williams Ltd.: Zr, 33·5; NO_3, 45·4%; $Zr : NO_3 = 0·736$. Calc. for $ZrO(NO_3)_2.2H_2O$: Zr, 34·1; NO_3, 46·5%; $Zr : NO_3 = 0·736$.]

General reagents. All were of "AnalaR" grade.

Apparatus and Technique.—It was decided to measure the overall elution curves radiochemically

and to analyse certain of the mixed fractions by optical spectrography. The starting materials were irradiated for periods of up to 4 weeks in the Harwell pile, the important reactions being

$$^{94}Zr\ (n;\ \gamma)\ ^{95}Zr \xrightarrow[t_{1/2}=65\text{ d.}]{-\beta} {}^{95}Nb \xrightarrow[t_{1/2}=35\text{ d.}]{-\beta} {}^{95}Mo$$

$$^{96}Zr\ (n;\ \gamma)\ ^{97}Zr \xrightarrow[t_{1/2}=17\text{ hr.}]{-\beta} {}^{97}Nb \xrightarrow[t_{1/2}=75\text{ min.}]{-\beta} {}^{97}Mo$$

$$^{180}Hf\ (n;\ \gamma)\ ^{181}Hf \xrightarrow[t_{1/2}=45\text{ d.}]{-\beta} {}^{181}Ta$$

It was found that the activity produced by the 65-day zirconium isotope (^{95}Zr) was too low and, consequently, in most of the separation experiments described, use has been made of the 17-hr. ^{97}Zr activity which has a higher β-particle energy and requires shorter irradiation periods in the pile.

The apparatus consisted essentially of a reservoir at the head of a glass column packed with cation-exchange material, shown in Fig. 1. The outlet at the base of the column led through a radioactivity-

FIG. 1.

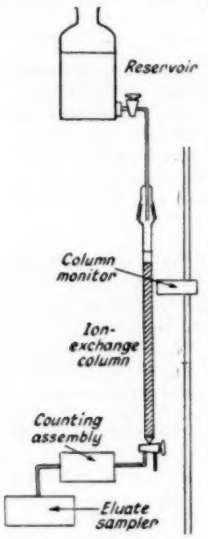
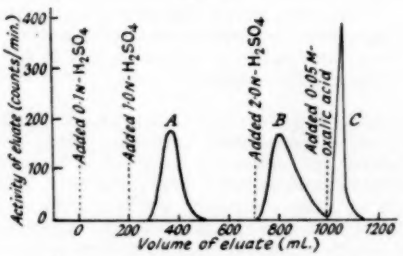


Diagram of separation apparatus.

FIG. 2.



Elution with 0·1, 1·0, *and* 2·0N-H_2SO_4: *load* ca. 15 *mg. of* ZrO_2.

counting assembly with recorder, and finally to an automatic eluate sampler. Three columns were used in the separation experiments: (1) 60 cm. × 0·8 cm. diameter holding *ca.* 20 g. of resin (mesh size 200—250); (2) 60 cm. × 1 cm. diameter holding *ca.* 30 g. of resin (mesh size 60—100); (3) for later larger-scale runs, the column size was increased to 120 cm. long and 2·5 cm. diameter to hold about 350 g. of resin (particle size about 0·5 mm. diameter).

To enable the weak-energy β-particles to be counted, a thin window liquid-flow counter was needed. A suitable cell was constructed by making a shallow zig-zag channel (*ca.* 0·02" deep) in a Perspex block and covering this with a thin Distrene sheet (thickness 2 mg./cm.^{2}) cemented on to the block with a very thin layer of black wax. The groove, which had a total length of 24 cm. and held about 0·2 ml. of liquid, was centred beneath an end-window type Geiger–Müller counter and a suitable filter interposed to remove the weak niobium activity (a daughter product of ^{95}Zr). The whole was enclosed within a 2" lead-walled castle.

Output pulses from the counter were passed *via* a pre-amplifier into a rate-meter circuit coupled to a four-pen recorder and a relay control unit. The rate-meter circuit consisted of three separate linear rate-meters whose ranges were 0—10, 0—100, and 0—1000 pulses per second, respectively. Each was coupled to a separate pen on the recorder, and readings of the activity could be made from the most convenient trace. The fourth pen on the recorder gave information on bottle changes. Complete details of the counting and liquid sampling mechanism will be published soon (Bennett and Whyard).

The activity at points along the column was determined by using a brass-screened end-window counter (connected to a scaling system) designed to receive a collimated beam of activity and able to

move up and down a vertically calibrated bar. Activity–column position curves constructed from such measurements have been termed " profile " curves and are a very valuable guide to the progress down the column of the uneluted portion of the activity.

Principle of the Method.—Ion-exchange materials can be used in two ways to effect separation: (*a*) the specificity of the exchange resin for one or other of the ions can be utilised, or (*b*) the resin can merely act as a second phase, and the main factor in the separation is the difference in the solution equilibria. In the present case, the second of these alternatives is being employed and the type of cation-exchange resin used is in no way specific for the separation.

Impregnation Procedure.—As a starting point in the separation experiments it was decided to use Street and Seaborg's impregnation method (*loc. cit.*) although this was later modified. 50 mg. of pile-irradiated " Specpure " zirconium oxide were dissolved with gentle warming in a mixture of 15 ml. of sulphuric acid and 15 ml. of 40% hydrofluoric acid. The solution were evaporated to dryness and the crystalline sulphate produced was dissolved with warming in 5 ml. of concentrated hydrochloric acid. After precipitation with ammonia solution, the hydroxide was centrifuged off, washed several times with water, and redissolved in hydrochloric acid. The oxychloride was crystallised from this solution. The product was dissolved in 5 ml. of 2N-perchloric acid, and the solution was slowly added (15 minutes) to an air-agitated suspension of 1 g. of Dowex 50 in 25 ml. of 2N-perchloric acid. When the addition was complete, the slurry was transferred to the top of a 60-cm. column of Dowex 50, the resin allowed to settle, the supernatant liquor removed as completely as possible, and the elution started. According to Street and Seaborg, absorption from 2N-perchloric acid overcomes difficulties due to polymerisation of the zirconium species and the uptake is about 80% complete (in the author's experience the uptake is not quite as high as this).

This procedure was later modified, the active zirconium-containing solution being fed slowly through a small subsidiary column of Dowex 50. After this column had been washed with N/2-perchloric acid, its content was transferred as a slurry to the top of the main column.

In the later stages of the work, it was found that absorption of zirconium from 2N-nitric acid solution was more efficient than from perchloric acid, and the impregnation procedure was altered accordingly.

Results.—Although other acid eluants have been used, namely, hydrochloric, nitric, perchloric, and oxalic acids of varying concentrations, by far the most satisfactory method for the separation of zirconium and hafnium depends on elution with sulphuric acid.

Sulphuric acid eluant. According to Connick and McVey (*J. Amer. Chem. Soc.*, 1949, **71**, 3182), sulphuric acid forms complexes quite strongly with zirconium (anion complexes are known to be formed) and one would expect a more rapid rate of elution than with other strong acids. A run was made in the 30-g. column in which the concentration of sulphuric acid eluant was increased stepwise from 0·1 to 1·0N., and then to 2·0N., the flow rate being kept constant at 40 ml./hour. With 0·1N-acid no movement of the zirconium–hafnium band (containing *ca.* 14 mg. of oxide) was observed after 200 ml. At this point, N-acid was added and a breakthrough of activity was observed after 90 ml. The activity, after rising sharply, had again reached a background level after a further 200 ml. and remained there until 500 ml. of the 1N-acid had been passed (Fraction A). Profile measurements showed that substantial activity still remained on the column, and the eluant was changed to 2N-sulphuric acid. A rapid increase in activity of the eluate was observed and, after a maximum had been passed, a near background level was again reached after 300 ml. of eluate had been collected (Fraction B). At this point 0·05M-oxalic acid solution (which forms very strong complexes with zirconium and hafnium) was passed through the column and all residual activity was rapidly removed (Fraction C). The complete elution curve is shown in Fig. 2. Precipitation with ammonia solution followed by ignition yielded 12·4 mg. of oxides from Fraction A (containing $<0{\cdot}1\%$ of hafnium); no visible precipitate was obtained by addition of ammonia solution to Fractions B and C, in spite of their considerable radioactivity, obviously due to hafnium. Thus an apparently complete separation of the two elements had been achieved with a very wide gap between the hafnium and the zirconium fractions. It is noteworthy that the order of separation is in the desired direction, the reverse of that obtained by Street and Seaborg's hydrochloric acid elution method and by the two published anion-exchange methods.

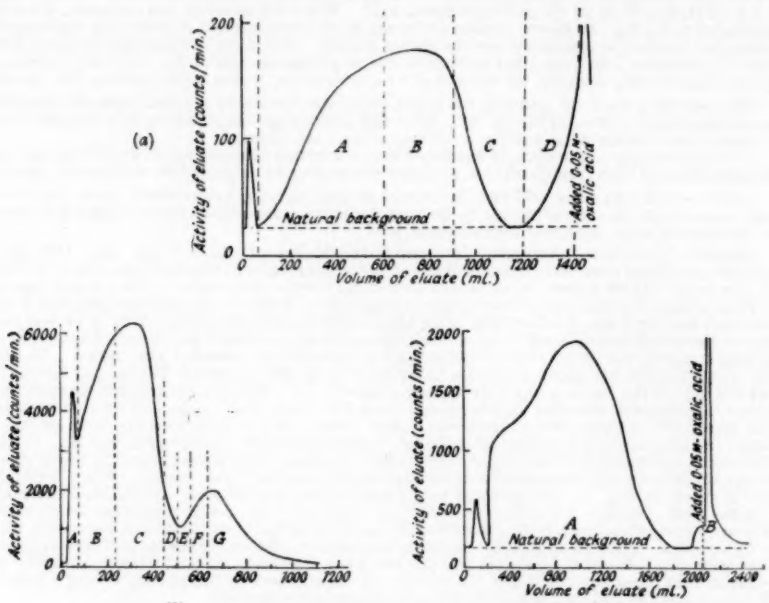
Experiments were made to find the maximum load which could be successfully treated on this column (containing 30 g. of Dowex 50) by elution with N-sulphuric acid. The practical limit was reached with a loading of 900 mg. of oxides. As shown in Fig. 3(*a*), the breakthrough point was 90 ml., and a background level of activity lasting for 30—40 ml. was reached after 1150 ml. The oxide precipitated from the eluate up to 1150 ml. was shown to contain $<0{\cdot}01\%$ of hafnium.

The uptake of zirconium from sulphuric acid solution by a cation exchanger has been shown to fall off rapidly with increase in acid concentration above 0·2N., and to be negligible above 1·5N. Thus small variations in acid concentration would probably cause considerable differences in the rate of elution from the column. The same column conditions being used as had been found just to give complete separation with N-acid, *i.e.*, a load of 900 mg. of oxide on the 30-g. column and a flow rate of 60 ml./hour, runs were made with 1·2N- and 0·8N-sulphuric acid eluant. With the stronger acid, as expected, a considerably more rapid elution was achieved but the separation was not quite complete. As shown in Fig. 3(*b*), activity between the two peaks was a minimum at about 500 ml. (compared with 1200 ml. with N-acid). An examination of the profile curves showed that the ratio of the volumes of the two acids required to cause the same movement of the hafnium peak was about 3 : 1. It is apparent that a complete separation could be achieved with a comparatively small decrease in loading. Such alteration of the conditions might possibly be advantageous to the rate of production of hafnium-free zirconium, but a greater number of runs would be necessary. The run with 0·8N-acid showed a much smaller rate of elution but with complete separation [see Fig. 3(*c*)].

An initial small peak has often been noticed before the main zirconium peak is eluted. This may be due to the rapid removal of adsorbed polymerised material as distinct from zirconium held on the resin by an exchange mechanism.

To investigate the possibility of treating larger amounts of material, a new column was constructed 120 cm. long and 2·5 cm. in diameter to hold about 10 times as much resin. Several changes in procedure were made. Dowex 50 resin was replaced by Zeokarb 225 (*ex* Permutit Co. Ltd.) which had been shown to be very similar to Dowex 50 in respect of both its capacity and its general exchange behaviour. The resin particle size was increased to about 0·5 mm. diameter to enable a higher flow rate to be used. To avoid disturbing the column, a simplified impregnation procedure was adopted whereby the zirconium solution was allowed to percolate very slowly through the main column, the activity being absorbed on the top section. The use of zirconyl nitrate instead of chloride enabled irradiated material to be used directly in the impregnating solution without the need for disposing of radioactive chlorine daughter products in this "*in situ*" impregnation method. Further, it was shown that the absorption of zirconium on a resin column from 2N-nitric acid was rather more efficient than from 2N-perchloric acid, and an alteration in this direction was made. For the higher flow rates needed in this column, the thin window counting assembly was replaced by a more robust internal spiral liquid-flow counter with a glass wall thickness of *ca.* 40 mg./cm.^{2}

FIG. 3.



Elution with sulphuric acid : (*a*) 1·0N, (*b*) 1·2N, (*c*) 0·8N. *Load* ca. 900 *mg. of* ZrO_2.

Thus a solution of 20 g. of zirconyl nitrate (containing 1 g. of neutron-irradiated "Specpure" zirconyl nitrate) in 1 l. of 2N-nitric acid was allowed to percolate very slowly through the column, and the absorbed material was eluted with N-sulphuric acid at a flow rate of 100 ml./hour. The profile curves of the hafnium activity are shown in Fig. 4. Hafnium started to appear in the eluate after about 9 l. of eluant had been passed, and spectrographic analysis of the oxide products obtained before this point showed <0·01% of hafnium. About 95—98% of the zirconium was recovered with this purity.

Breakthrough Technique.—A disadvantage of the elution chromatography technique is the number of stages involved. A more useful separation method is the "breakthrough" technique whereby the mixture to be separated, dissolved in a suitable solvent, is passed through a column of resin, the mixture being continually fed in as the run proceeds. This method cuts out the impregnation step and so considerably simplifies the procedure.

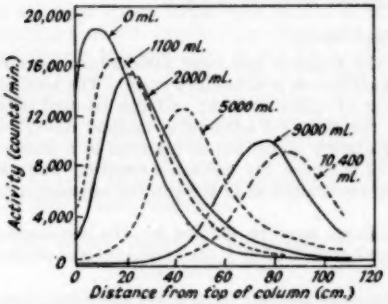
The possibility of using the "breakthrough" technique in the present case was investigated by passing through the large (350-g.) column a solution containing 2·5 g. of zirconyl nitrate per l. of N-sulphuric acid at a flow rate of about 200 ml./hour. Fractions of the effluent from the column were collected, the hydroxides precipitated and ignited, and the oxides examined spectrographically for hafnium. It is seen from Fig. 5 that a small quantity of zirconium and hafnium leak through into the effluent almost immediately, this concentration remaining approximately constant until the main zirconium breakthrough point at about 9 l. Over this initial portion the hafnium–zirconium ratio remains quite high at about the value of the in-going solution. The concentration of hafnium in the effluent remains

sensibly constant until it begins to rise rapidly at about 18 l. (*i.e.*, when 10 g. of mixed oxides have passed through the column). Up to this point the oxides precipitated from the effluent contained overall *ca.* 0·1% of HfO_2. The first 8·2 g. of oxides had an overall HfO_2 content of 0·047%. The drop in zirconium content towards the end of the run is probably due to a fall in the flow rate. The slow uptake of zirconium was indicated by the decrease in effluent concentration noted at two points in the run after the flow had been stopped for some hours.

Thus, although the method is convenient and efficient for producing a low hafnium-content zirconium oxide, it does not give the clean separation achieved by the elution method for the same amount of material processed.

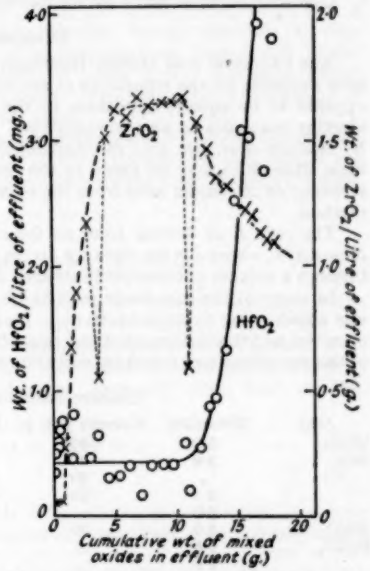
Purification of Hafnium.—A sample of 70 mg. of hafnium oxide was converted into oxychloride and absorbed on the 30-g. column as previously described for zirconium. Spectrographic analysis indicated the presence of about 8% of zirconium oxide and it was hoped, by elution with N-sulphuric acid, to

FIG. 4.



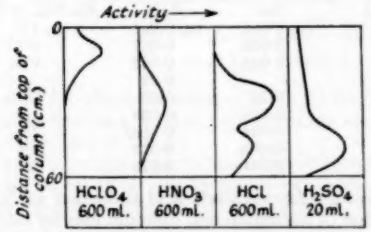
Profile curves of hafnium activity during elution with 1N-H_2SO_4. *Load: 9 g. of* ZrO_2 *on 350-g. column.*

FIG. 5.



Effluent curves for "breakthrough" run using 1N-H_2SO_4 *solution.*

FIG. 6.



Comparison of profile curves for 3N-*acid eluants.*

purify the hafnium oxide from this contaminant. Breakthrough of hafnium activity was observed after 675 ml.; 6 mg. of oxides were obtained from the eluate up to this volume, and oxalic acid treatment of the column produced a further 63 mg. of oxide which was shown to be substantially free from zirconium.

Experiments with Other Acids as Eluants.—Other acid eluants were not as satisfactory as sulphuric acid for the separation, but it is interesting to compare the results obtained.

Hydrochloric acid eluant. Under the same conditions as those used by Street and Seaborg, *i.e.*, elution with 6N-hydrochloric acid, some separation was apparent from the elution and profile curves, but the elution was far too rapid for good resolution to be achieved.

A slower rate of elution was found with 3N-hydrochloric acid. The flow rate was maintained constant at 8 ml./hour, and the activity of the eluate started to rise after about 370 ml. After 67 hours the activity was again at background level after having passed through a maximum, and the residual activity on the column was stripped with 0·05M-oxalic acid solution. No hydroxide precipitate was obtained from the solution before oxalic acid treatment, but 10 mg. of oxide (corresponding to the loading of the column) were obtained from the oxalic acid fraction. Spectrographic analysis of this oxide showed a hafnium content of 0·14%.

Similar results were obtained with a 10-fold increase in the loading, the first 10 mg. of oxide precipitated from the eluate having an increased hafnium content of 3·1%.

Oxalic acid eluant. Results obtained while stripping residual activity from the column with oxalic acid indicated that separation might be achieved, with zirconium coming first from the column, by using dilute oxalic acid as eluant. Runs were made with 0·01 and 0·001M-oxalic acid. Spectrographic analysis showed that hafnium was, in fact, held more strongly on the column, but the separation achieved was not as marked as with hydrochloric acid. With both concentrations of oxalic acid, very rapid breakthroughs were obtained at about 30 ml., followed by long " tails " in the elution curves.

Nitric acid eluant. Nitric acid has been reported by Connick and McVey (*loc. cit.*) to have similar complexing properties for zirconium to hydrochloric acid. However, elution with 3N-acid gave no apparent separation, although the single observed activity peak moved at a rate similar to that of the zirconium peak in runs with 3N-hydrochloric acid.

Perchloric acid eluant. Perchloric acid has been assumed to show the least inclination of the strong acids to complex with zirconium; and, indeed, elution with 3N-perchloric acid showed a very much slower rate of movement of the activity peak down the column than with the same concentration of nitric and hydrochloric acids. No separation was noticed.

Comparative profile curves for the four strong acids studied are shown in Fig. 6.

Summary and Discussion.

The sulphuric acid elution technique provides the simplest and most satisfactory method now available for the separation of zirconium and hafnium on a laboratory scale. The method appears to be equally applicable to the purification of either element and can be used with starting materials of any composition. Although the silica gel adsorption method described by Hansen *et al.* (*loc. cit.*) can apparently deal with larger quantities of material in a shorter time, difficulties may be found in the preparation of the very dry methanol required, and the recovery of zirconium salts from the eluate is not so convenient as in the present ion-exchange method.

The rate E of elution from an ion-exchange column may be defined by the expression $E = dA/V$, where d is the distance (in cm.) a band peak travels after V ml. of eluant have passed through a column of cross-sectional area A cm.^{2}.

In many of the runs made with hafnium and zirconium elution, no separate zirconium peak was noted owing to its low activity. However, in some cases the movement of both bands was observed and the elution constants could be calculated (see table). In other cases the movement of the zirconium was found by repeating the runs, only zirconium tracer being used.

Elution constants for zirconium and hafnium.

Acid	Normality	Column size, g.	Load (mg.)	E_{Zr}	E_{Hf}	$E_{Zr}/E_{Hf} = \bar{E}$
$HClO_4$	3·0	30	*ca.* 15	*ca.* 0·001	*ca.* 0·001	*ca.* 1·0
HCl	3·0	20	,,	0·038	0·067	0·57
,,		30	*ca.* 200	0·038	0·062	0·62
	4·5	20	*ca.* 15	—	0·34	—
	6·0	,,	,,	0·39	0·52	0·76
HNO_3	3·0	30	,,	0·038	0·038	*ca.* 1·0
H_2SO_4	0·8	,,	*ca.* 900	0·064	0·0133	4·8
	1·0	,,	,,	0·085	0·022	4·1
	1·2	,,	,,	0·181	0·069	2·7

The great difference between the elution constant for 3N-perchloric acid and other acids of the same concentration makes it clear that the elution of zirconium and hafnium ions by nitric, hydrochloric, and sulphuric acids is due to a complex action. The nature of this action has been made clearer by work on the solution chemistry of zirconium to be described in a later communication.

As would be expected, the degree of separation represented by the relationship $E_{Zr}/E_{Hf} = \bar{E}$ increases with decreasing acid concentration both in hydrochloric and in sulphuric acid solution, although the utility of reducing the acid concentration further gets progressively less. For example, with sulphuric acid the ratio of the $\bar{E}$ values between 1·2 and 1·0N. is about 1·5, while between 1·0 and 0·8N. it is only 1·17.

It is of interest that the elution constants for zirconium in 3N-hydrochloric and nitric acid solution are the same; no separation, however, is achieved with the latter while, with the former, $\bar{E} = ca.$ 0·6.

The breakthrough technique, although convenient and efficient for producing a low hafnium-content zirconium oxide, does not give the clean separation achieved by the elution method.

I am indebted to the Chemical Inspectorate, Woolwich, for all the spectrographic analyses, and I thank the Director of the Atomic Energy Research Establishment for permission to publish this paper.

Atomic Energy Research Establishment,
Harwell, Berks.

[*Received, June 27th,* 1951.]

692. *A Theoretical Treatment of the Diels–Alder Reaction. Part IV.* The Significance of Free-valence Numbers.*

By R. D. Brown.

By using the para-localization energy as a standard for comparison, the possibility of employing other theoretical quantities as criteria of Diels–Alder reactivity is examined. It is shown that the sum of the appropriate free-valence numbers provides an alternative index of reactivity, probably not quite as reliable as the localization energy.

It has been shown in previous papers of this series (*J.*, 1950, 691, 2730; 1951, 1612) that a molecular-orbital energy quantity termed the para-localization energy provides a very satisfactory interpretation of the Diels–Alder properties of hydrocarbons, particularly in the polycyclic series. In the present paper the possibility of using other molecular-orbital quantities as criteria of Diels–Alder reactivity is considered. The discussion is analogous to that recently given for bond reactivity (Brown, *J.*, 1951, 1950).

The formation of the Diels–Alder activated complex is accompanied by a partial localization of the π-electrons at a pair of *para*-orientated positions. If it is supposed that the effect of the approaching dienophile is to change the coulomb integral of these atoms then, Brown's notation (*J.*, 1951, 1950) being used:

$$\delta H_\pi = (\partial H_\pi/\partial\alpha_a)\delta\alpha_a + (\partial H_\pi/\partial\alpha_b)\delta\alpha_b + \tfrac{1}{2}[(\partial^2 H_\pi/\partial\alpha_a^2)(\delta\alpha_a)^2 + 2(\partial^2 H_\pi/\partial\alpha_a\partial\alpha_b)\delta\alpha_a\delta\alpha_b + (\partial^2 H_\pi/\partial\alpha_a^2)(\delta\alpha_b)^2] + \ldots \quad (1)$$

It is reasonable to assume that the perturbations $\delta\alpha_a$ and $\delta\alpha_b$ to the coulomb integrals of the attacked atoms a and b are equal. For convenience we shall write them as $X\beta$, so that the energy change will be expressed in terms of the resonance integral, β, as is usual in the molecular-orbital method. Further, we can identify the differential coefficients with electron densities, q, and mutual polarizabilities, π (Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, 1947, *A*, **191**, 39). With these substitutions (1) becomes

$$\begin{aligned}\delta H_\pi &= (q_a + q_b)X\beta + (\pi_{a,a} + 2\pi_{a,b} + \pi_{b,b})X^2\beta^2/2 + \ldots \\ &= (2X + TX^2/2 + \ldots)\beta \quad \ldots\ldots\ldots\ldots \quad (2)\end{aligned}$$

because for alternant hydrocarbons all the q are unity; for convenience T, which is a pure number, has been written for β times the second expression in parentheses (polarizabilities have the dimension of $1/\beta$).

If this perturbation to the coulomb integrals is the major effect of the dienophile, and if the higher terms of (2) can be neglected for the value of X corresponding to the transition state, then the pair of positions with the greatest value of T will correspond to the smallest activation

Table I.

Hydrocarbon	Position	$P(-\beta)$	T	Hydrocarbon	Position	$P(-\beta)$	T
Butadiene	1 : 4	2·47	0·716	Naphthalene	1 : 4	3·68	0·608
Hexatriene	1 : 4	2·99	0·713	Anthracene.....	1 : 4	3·63	0·607
	2 : 5	4·99	0·774		9 : 10	3·31	0·616
Benzene	—	4·00	0·593	Phenanthrene ...	1 : 4	3·77	0·627

energy and hence be most reactive. Some values of T are given in Table I. It is evident that T bears very little relationship to Diels–Alder reactivity. It is interesting that a similar state of affairs exists for bond reactivity (Brown, *J.*, 1951, 1950), so it appears that in both of these reactions *perturbations to the coulomb integrals are of minor importance.*

A perturbation corresponding more closely to the localization process envisaged in the formation of the transition state would be brought about by reduction in magnitude of the resonance integrals of all bonds around a and b (I). In this case if all perturbations are taken

* Part III, *J.*, 1951, 1612.

to be $X\beta$, and the differential coefficients are expressed in terms of mobile bond orders, p, and bond polarizabilities, the Taylor series becomes

$$\delta H_\pi = (UX + VX^2 + \ldots)\beta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where U and V represent

$$U = 2(p_{ca} + p_{ad} + p_{fb} + p_{be}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$V = (\pi_{ca,ca} + \pi_{ad,ad} + \pi_{fb,fb} + \pi_{be,be} + 2\pi_{ca,ad} + 2\pi_{ca,fb} + 2\pi_{ca,be} + 2\pi_{ad,fb} + 2\pi_{ad,be} + 2\pi_{fb,be})\beta \quad . \quad . \quad (5)$$

Suppose that, owing to X, V, or both, being sufficiently small, only the first term in (3) is significant for the value of X corresponding to the transition state. Then, since X must be negative, the smallest increase in the π-electron energy, *i.e.*, the smallest activation energy, will occur for the pair of positions for which the sum of bond orders, U, is *least*. Values of U for a number of hydrocarbons are listed in Table II.

(I)

There is seen to be quite a close correspondence between P and U, small values of P going with small values of U as required. However, there are some irregularities, the most important being the comparative figures for the 9 : 10-positions of anthracene and benzanthracene. The para-localization energies predict anthracene to be the more reactive, in accordance with experimental observation (*e.g.*, Bachmann and Kloetzel, *J. Amer. Chem. Soc.*, 1938, **60**, 481). On the other hand the relative values of U would lead one to expect the opposite relative reactivites. This discrepancy must be due to the neglect of V and the higher coefficients in (3).*

TABLE II.

Hydrocarbon	Position	$P(-\beta)$	U	Hydrocarbon	Position	$P(-\beta)$	U
Benzene	—	4·00	5·33	Picene	1 : 4	3·75	5·15
Naphthalene	1 : 4	3·68	5·12	1 : 2-Benzanthracene	1′ : 4′	3·78	5·15
					9 : 10	3·41	4·83
Anthracene	1 : 4	3·63	5·09		5 : 8	3·64	5·10
	9 : 10	3·31	4·85				
				1 : 2-3 : 4-Dibenzanthracene	1′ : 4′	3·83	5·17
Naphthacene	1 : 4	3·62	5·08		9 : 10	3·49	4·93
	5 : 12	3·25	4·81		5 : 8	3·70	5·10
Pentacene	1 : 4	3·61	5·08	1 : 2-5 : 6-Dibenzanthracene	1′ : 4′	3·79	5·15
	5 : 14	3·23	4·80		9 : 10	3·51	4·94
	6 : 13	3·18	4·77				
				1 : 2-7 : 8-Dibenzanthracene	1′ : 4′	3·79	5·15
Phenanthrene	1 : 4	3·77	5·14		9 : 10	3·51	4·94
	4 : 5	4·37	5·17				
				Pentaphene	1 : 4	3·67	5·10
Chrysene	3 : 6	3·74	5·14		5 : 14	3·45	4·90
3 : 4-Benzophenanthrene	1′ : 4′	3·74	5·14				

To illustrate the order of magnitude of V some values are listed in Table III. Although small compared with U, V is seen to be by no means negligible, and although the data in Table III are too meagre to lead to a definite conclusion, it would appear that V increases

TABLE III.

Hydrocarbon	Position	V	$P(-\beta)$	U
Benzene	1 : 4	0·296	4·00	5·33
Naphthalene	1 : 4	0·374	3·68	5·12
Styrene	2 : 5	0·322	3·95	5·25

with decreasing P or U. Obviously the good correlation between P and U must be attributable in part to further monotonic relationships between V and P, and perhaps to higher coefficients also.

* *Added in Proof.*—Dr. H. H. Greenwood has kindly informed me that this discrepancy is due to an error in the published bond-order data for benzanthracene (*Compt. rend.*, 1948, **226**, 1906). The corrected value for the 9 : 10-positions is $U = 490$.

The preceding discussion of U as a criterion of Diels–Alder reactivity leads directly to free valence in the following way. The free valence of an atom a is defined by the relation

$$F_a = N_{max.} - \Sigma_i p_{ai} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where the summation is over all atoms, i, adjacent to a, and $N_{max.}$ is some arbitrary constant which has been given various values in the literature, the two most popular being 1·680 and $\sqrt{3}$. From (4) and (6) it is obvious that

$$U = 4N_{max.} - 2(F_a + F_b) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Consequently if U is a criterion of Diels–Alder reactivity then ΣF is also. Moreover a high value of ΣF will correspond to a high reactivity. Since ΣF and U are related by (7) there is no point in listing values of the former in Table II, and of course the same discrepancy between the reactivities of anthracene and benzanthracene will still be present. A disadvantage in using free-valence data from the literature is that one has to be careful that all values correspond to the same value of $N_{max.}$. It is partly for this reason that we have chosen to discuss mainly U in the above treatment rather than the more familiar ΣF.

Evans (*Trans. Faraday Soc.*, 1946, **42**, 113) and Diatkina and Syrkin (*Acta Physicochim.*, 1946, **21**, 921) have found approximate linear correlations between quantities equivalent to para-localization energies and oxidation–reduction potentials of the corresponding *p*-quinones. This of course means that there will be a correlation between the latter and the Diels–Alder reactivity, similar to the correlation of oxidation–reduction potentials of *o*-quinones with bond reactivity (Brown, *J.*, 1951, 1950). However this does not mean that the transition state is quinonoid in structure; rather it implies that the quinone oxidation–reduction potentials can be related to the π-electron energies of *essentially non-quinonoid conjugated systems*. The correlation of the experimental oxidation–reduction potential with para-localization energy is not particularly good so we cannot expect this experimental quantity to be of very great value as an index of Diels–Alder reactivity.

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WHEATSTONE PHYSICS DEPARTMENT,
KING'S COLLEGE, STRAND, LONDON, W.C.2.

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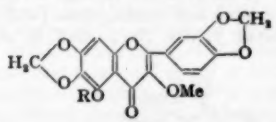
693. *Chemistry of New Zealand* Melicope *Species. Part VI.* A Revised Constitution for Meliternatin, and the Identification of Xanthoxyletin from the Bark of* Melicope ternata.

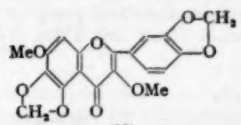
By LINDSAY H. BRIGGS and R. H. LOCKER.

Further evidence has been adduced for the revised formulation of meliternatin as 3 : 5-dimethoxy-6 : 7-3′ : 4′-bismethylenedioxyflavone. "Compound E," the non-flavone substance isolated from *Melicope ternata*, has been identified as xanthoxyletin.

IN Part I of this series (*J.*, 1949, 2157) a fully alkylated flavonol, meliternatin, from the bark of *Melicope ternata*, was shown to contain two methoxyl groups (one at $C_{(3)}$), and two methylenedioxy-groups. Hydrolysis with alcoholic potassium hydroxide yielded three phenolic



(I)



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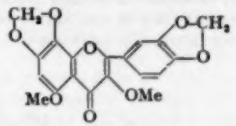
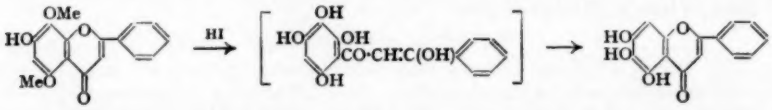


(III)

substances and piperonylic acid, this acid establishing the nature of the side phenyl group. Three formulæ (I; R = Me), (II), and (III) were considered on this basis.

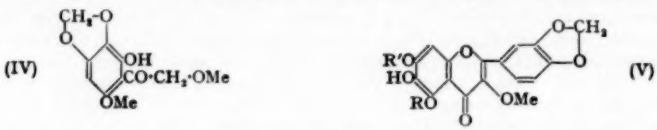
* Part V, *J.*, 1950, 2379.

Dealkylation with hydriodic acid afforded quercetagetin (3 : 5 : 6 : 7 : 3′ : 4′-hexahydroxyflavone), supporting a structure (I; R = Me) or (II) for meliternatin. However, by an apparent process of ring opening and closing, certain 5 : 8-dimethoxyflavones on demethylation form 5 : 6-dihydroxy-derivatives although, so far, the reverse transformation has not been observed (for a summary see Shah, Mehta, and Wheeler, *J.*, 1938, 1555; cf. also Baker,



J., 1939, 956; Baker and Simmonds, *J.*, 1940, 1370; Sastri and Seshadri, *Proc. Indian Acad. Sci.*, 1946, **24**, 243). For this reason a formula (III) could not be excluded for meliternatin.

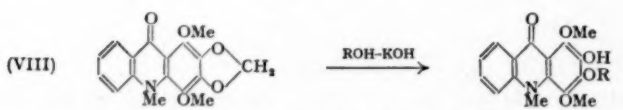
The main phenol arising from the hydrolysis had the expected properties of a 2-hydroxy-*x* : ω-dimethoxy-methylenedioxyacetophenone. It gave a positive test with 2 : 6-dibromoquinonechloroimide (Gibbs, *J. Biol. Chem.*, 1927, **72**, 649), indicating a free position *para* to the phenolic group. This supported a structure (IV) for the phenol and (III) for meliternatin.



Further evidence, however, now definitely precludes formula (III) and supports (I; R = Me) rather than (II) for meliternatin.

In the alkaline hydrolysis of meliternatin with alcoholic potassium hydroxide, a second phenolic compound, m. p. 194—195°, was isolated in small yield for which a tentative formula, $C_{10}H_{10}O_4$, was given, with the observation that its composition did not correspond with that of any of the expected products. In making a survey of the absorption spectra of flavonols related to this series of investigations (succeeding paper), we measured that of the above phenolic compound and found that it was practically indistinguishable from that of 6-hydroxy-3 : 5 : 7-trimethoxy-3′ : 4′-methylenedioxyflavone (V; R = R′ = Me) obtained synthetically (Part V, *J.*, 1950, 2379). The phenolic compound gives the reduction tests for a flavonol methylated at $C_{(3)}$, but the analytical figures now equally fit the empirical formula, $C_{20}H_{18}O_8$, with two methoxyl groups. This compound was formed, we considered, by fission of the methylenedioxy-group in the benzo-nucleus under the activating influence of the carbonyl group at $C_{(4)}$. Robinson and Robinson (*J.*, 1917, **111**, 109, 929) have shown that a solution of a sodium alkoxide in the corresponding alcohol readily converted 4-nitrocatechol methylene ether (VI) into the 4-nitrocatechol 1-alkyl ether (VII), and Parijs (*Rec. Trav. chim.*, 1930, **49**,

41) obtained a similar result with the 4 : 5-dinitro-derivative. A much closer parallel to the present case is the fission of the methylenedioxy-group of melicopine and melicopidine (VIII) with alcoholic potassium hydroxide (Crow and Price, *Australian J. Sci. Res.*, 1949, **2**, *A*,

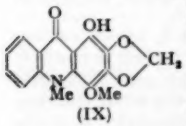


255, 282; cf. also evoxanthine, Hughes and Neill, *ibid.*, p. 429). That this view of the mechanism was correct was shown by the fact that the action of sodium methoxide on

meliternatin afforded 6-hydroxy-3 : 5 : 7-trimethoxy-3′ : 4′-methylenedioxyflavone (V; R = R′ = Me), identified by mixed melting points of the free compounds and their acetates. Since this reaction does not affect the position of the oxygen atoms meliternatin must therefore be a 5 : 6 : 7-derivative and not a 5 : 7 : 8-derivative. This excludes formula (III), and meliternatin must then be either (I; R = Me) or (II). The above reactions with alcoholic alkali do not enable a distinction to be made between (I; R = Me) and (II). Positions 5 and 7 are both activated by the carbonyl group at $C_{(4)}$ and the action of alcoholic potassium hydroxide on (I; R = Me) and (II) would give (V; R = Me, R′ = Et) and (V; R = Et, R′ = Me) respectively, probably indistinguishable in their absorption spectra from their methyl analogues. The same product (V; R = R′ = Me) would be obtained from both (I; R = Me) and (II) by the action of sodium methoxide.

In Part I (*loc. cit.*) we reported that the action of aluminium chloride on meliternatin in nitrobenzene at 100° formed an aluminium lake from which the metal could not be removed. Under milder conditions, with an excess of aluminium chloride in boiling ether, meliternatin was smoothly demethylated to a yellow, monohydric flavonol, $C_{14}H_{12}O_8$, forming a monoacetate and still containing one methoxyl group and giving a positive methylenedioxy-test. Although an absolute proof cannot be given for this substance the following accumulated evidence supports the formula (I; R = H), and hence (I; R = Me) rather than (II) for meliternatin.

Baker (*J.*, 1939, 961; Baker, Brown, and Scott, *ibid.*, p. 1922; Baker and Simmonds, *J.*, 1940, 1373) has shown that 5-methoxyflavones undergo demethylation with aluminium chloride in boiling ether, and Shah, Virkar, and Venkataraman (*J. Indian Chem. Soc.*, 1942, **19**, 135) have reported that 3-methoxyflavone is not demethylated by aluminium chloride at room temperature but is at 100°. In Part V (*loc. cit.*) we have shown that aluminium chloride in boiling ether demethylates melisimplexin (3 : 5 : 6 : 7-tetramethoxy-3′ : 4′-methylenedioxyflavone) to melisimplin. While no definite proof can be given for the constitution of the latter its colour reactions favour a 5-hydroxy-3 : 6 : 7-trimethyl-3′ : 4′-methylenedioxyflavone structure. This is supported on the phytochemical grounds that no naturally occurring 3 : 5-dihydroxyflavone exists which is methylated at $C_{(5)}$ but not at $C_{(3)}$. Our experiment, we believed therefore, supported those of Baker in that aluminium chloride in boiling ether was apparently a specific reagent for the demethylation of flavones methoxylated at $C_{(5)}$. We have now shown, however, that quercetin pentamethyl ether is demethylated by aluminium chloride in boiling ether to quercetin 5 : 7 : 3′ : 4′-tetramethyl ether, *i.e.*, demethylation has occurred at $C_{(3)}$. The reaction is therefore not specific for the $C_{(5)}$ position but may occur at $C_{(3)}$ or $C_{(5)}$ according to factors still unknown. Quercetin pentamethyl ether may, however, be demethylated at $C_{(5)}$ by using the technique of Crow and Price. They have shown (*Australian J. Sci. Res.*, 1949, **2**, *A*, 260) that acridone alkaloids methoxylated at $C_{(4)}$ are demethylated specifically at this point when they are heated with alcoholic hydrochloric acid or when their hydrochlorides are heated above their melting points, *e.g.*, the conversion of melicopidine (VIII) into normelicopidine (IX).



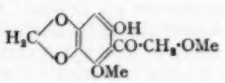
(IX)

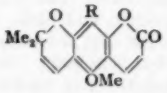
There are formal similarities between these alkaloids and fully alkylated flavonols which are reflected in their properties [cf. the basic properties of meliternatin recorded in Part I (*loc. cit.*) and the discussion in the succeeding paper]. Quercetin pentamethyl ether is also basic, readily forming coloured salts such as the hydrochloride (Watson, *J.*, 1914, **105**, 338). The pentamethyl ether may be recovered unchanged after treatment with alcoholic hydrochloric acid but when the hydrochloride is heated above its melting point it is smoothly converted into quercetin 3 : 7 : 3′ : 4′-tetramethyl ether. The specificity of these demethylating methods is worth further study.

On the above evidence, the demethylated meliternatin could have its free hydroxyl group at $C_{(3)}$ or $C_{(5)}$ if derived from (I; R = Me), or only at $C_{(3)}$ if derived from (II). The following properties of the compound definitely favour a free hydroxyl at $C_{(5)}$ rather than at $C_{(3)}$. Acid or alkaline reduction of the demethylated product gives a pink colour showing that the remaining methoxyl group is at $C_{(3)}$ (cf. Part I, *loc. cit.*). It gives a green colour with ferric chloride in alcohol. Both 5- and 3-hydroxyflavones give intense ferric chloride colours but the colours given by the 5-hydroxy-compounds are almost invariably green (cf. Seshadri and his co-workers, *Proc. Indian Acad. Sci.*, 1941, **14**, 290; 1945, **22**, 385; 1946, **23**, 299; 1946, **24**, 377, 457; 1947, **25**, 339, 402; 1947, **26**, 15, 19, 75, 214, 235; 1950, **31**, 33) and occasionally brown (Row and Seshadri, *ibid.*, 1945, **22**, 220) or purple (Rajagopalan, Rao, and Seshadri, *ibid.*, 1947, **25**, 436) while the colour given by 3-hydroxyflavones is, to our knowledge, invariably brown (cf. Seshadri and his co-workers, *ibid.*, 1945, **21**, 131; 1946, **23**, 99; 1946, **24**, 377, 457;

1947, **28**, 192; 1949, **30**, 216). The demethylated product shows no fluorescence in organic solvents. Fluorescence is a characteristic of 3-hydroxyflavones but not of 5-hydroxyflavones (Seshadri and Venkateswarlu, *ibid.*, 1947, **26**, 190; Seshadri and his co-workers, *ibid.*, 1945, **21**, 131; 1946, **23**, 99; 1949, **30**, 216). The demethylated product is insoluble in sodium hydroxide solution. The 5-hydroxyflavones quoted above are all recorded as insoluble or sparingly soluble in sodium hydroxide solution while the 3-hydroxyflavones quoted are recorded as soluble or sparingly soluble, not one example being noted as insoluble. The solubility of the demethylated product in concentrated hydrochloric acid is in agreement with its formulation as a 5-hydroxyflavone (cf. the succeeding paper) but there is insufficient evidence of the behaviour of 3-hydroxyflavones for this test to be of much value. Mordanted wool is dyed by the demethylated product but this is explicable by the presence of a hydroxyl group at either $C_{(5)}$ or $C_{(3)}$.

The accumulated evidence above supports the presence of a free hydroxyl group at $C_{(5)}$ for the demethylated product, *i.e.*, formula (I; R = H), and thus formula (I; R = Me) for meliternatin. Consequent on this, the product of the action of alcoholic potassium hydroxide on meliternatin has the formula (V; R = Me, R′ = Et) and the main phenol, m. p. 142—144°, arising from the hydrolysis of meliternatin, is most probably 6-hydroxy-2 : ω-dimethoxy-3 : 4-methylenedioxyacetophenone (X). The positive test given with 2 : 6-dibromoquinonechloro-

(X) 


(XI)

imide may be due to an impurity (the test is very sensitive, detecting phenol itself at a concentration of 1 in 2×10^7). In contrast, it is surprising that 2 : 4 : 6-trihydroxy-ω-methoxy-acetophenone and 2-hydroxy-4 : 6 : ω-trimethoxyacetophenone, both of which have free positions *para* to phenolic groups, do not give positive tests with this reagent.

In Part I (*loc. cit.*) a tentative structure, 5 : 3′ : 4′-trihydroxy-3-methoxy-7 : 8-methylenedioxyflavone, was proposed for wharangin. This was based solely on colour reactions and on the phytochemical grounds that the other three flavonols accompanying it, *viz.*, meliternatin, meliternin, and ternatin, were all 5 : 7 : 8-derivatives. The revised formulation for meliternatin as a 5 : 6 : 7-derivative now removes these phytochemical grounds and allows for further possible structures for wharangin.

Accompanying the four flavonols in the bark of *Melicope ternata* (Part I, *loc. cit.*) was a colourless compound, " Compound E," m. p. 133·5—134°, which was not a flavone derivative. A tentative formula, $C_{15}H_{16}O_4$, was proposed for this substance which did not react with ferric chloride, but gave a positive methylenedioxy-test overnight. Apart from the latter reaction, the properties of this compound corresponded with those of xanthoxyletin (XI; R = H), $C_{15}H_{14}O_4$, from the related species of *Rutaceæ*, *Xanthoxylum americanum* (prickly ash). This was first isolated by Staples (*Amer. J. Pharm.*, 1829, 163), and its constitution has been elucidated by Robertson and his co-workers (*J.*, 1936, 627; 1937, 286). The combustion figures of our compound agreed equally well with those for $C_{15}H_{14}O_4$ and a direct comparison, by mixed melting point with an authentic sample of xanthoxyletin, kindly provided by Professor A. Robertson, showed that they were identical. The positive methylenedioxy-test is probably due to a trace of impurity (the test is only given overnight whereas the colour from methylenedioxy-compounds normally appears within half an hour) and the following bromo-derivative did not give it.

Gordin (*J. Amer. Chem. Soc.*, 1906, **28**, 1649) brominated xanthoxyletin in acetic acid to a dibromide monohydrate, crystallising from acetone–alcohol in colourless " warts," m. p. 171°. In seeking to confirm the identification of our compound with xanthoxyletin we brominated both compounds in chloroform. The products were identical (mixed melting point), but they were different (m. p. 157·5—158·5°) from that obtained by Gordin and corresponded to a monosubstituted derivative which we consider is (XI; R = Br) although it gives an inexplicably high analytical value for hydrogen. The monobromo-derivative gives an unusual colour reaction with concentrated sulphuric acid, the crystals becoming blue, then green, before dissolving to a yellow solution.

Xanthoxyletin exhibits absorption peaks (log ε in parentheses) at 227 (4·28), 269 (4·32), 322 (3·99) and 347 (4·05) when measured in *ca.* M/20,000 alcoholic solution.

Experimental.

(M. p.s are corrected.)

The analyses are by Drs. Weiler and Strauss, Oxford, and Dr. T. S. Ma, Microchemical Laboratory, University of Otago, Dunedin.

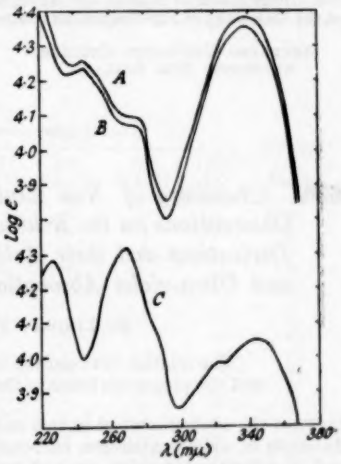
Demethylation of Meliternatin with Aluminium Chloride.—Meliternatin (300 mg.) was refluxed with a solution of freshly prepared aluminium chloride (4 g.) in dry ether (16 c.c.) for 10 hours. The yellow precipitate formed when the mixture was poured into water was boiled for 20 minutes with acetic acid (20 c.c.) and concentrated hydrochloric acid (10 c.c.). The precipitate which formed on dilution of the mixture with water (150 c.c.) crystallised from acetone in light mustard-coloured needles, m. p. 253—255° (147 mg.). Two further crystallisations raised the m. p. to 258—258·5° (Found : C, 60·9; H, 3·4; OMe, 6·2. $C_{18}H_{12}O_8$ requires C, 60·7; H, 3·3; 1OMe, 8·7%). The *substance* is insoluble in 10% sodium hydroxide solution and concentrated hydrochloric acid but soluble in concentrated sulphuric acid with a bright yellow colour, becoming green on addition of gallic acid. Ferric chloride solution produces a light green colour and acid or alkaline reduction a pink colour.

The demethylated product (22 mg.) was acetylated, for ½ hour, with an excess of acetic anhydride containing one drop of 60% perchloric acid. After addition of water, the precipitated solid *acetate* formed slightly yellow needles, m. p. 208·5—210° (15 mg.) when crystallised twice from alcohol (Found : C, 60·4; H, 3·8. $C_{20}H_{14}O_9$ requires C, 60·3; H, 3·5%).

A sample of wool mordanted with potassium dichromate and tannic acid was dyed by immersing it in a boiling aqueous suspension of the demethylated product for an hour. The wool was dyed a pale yellow colour, unchanged after 20 minutes' boiling with fresh water; the colour was identical with that produced by melisimplin, of similar constitution [cf. Parts IV (*J.*, 1950, 2376) and V (*loc. cit.*)], under similar conditions.

Hydrolysis Product from Meliternatin.—The compound, m. p. 194—195°, described in Part I (*loc. cit.*) as one of the hydrolytic products of meliternatin, and now recognised as 6-hydroxy-3 : 5 : 7-trimethoxy-3′ : 4′-methylenedioxyflavone, has been re-analysed (Found : C, 61·9; H, 4·7; OMe, 11·6. Calc. for $C_{20}H_{18}O_8$: C, 62·2; H, 4·7; 1OMe, 12·5%). Reduction with magnesium and hydrochloric acid gave an orange-red colour; sodium amalgam gave a yellow solution which became pink on acidification.

Action of Sodium Methoxide on Meliternatin.—A solution of meliternatin (200 mg.) in absolute methyl alcohol (40 c.c.) was heated under reflux for 2 hours with sodium methoxide solution [2·4 c.c. of a solution obtained by dissolving sodium (3 g.) in absolute methyl alcohol (30 c.c.)]. On cooling, large amounts of meliternatin crystallised out. The remainder of the sodium methoxide was added (making a 13% solution) and the heating continued for 6 hours. On cooling, nothing separated from the bright yellow solution which was then made slightly acid with hydrochloric acid and taken almost to dryness on the water-bath. Part of the colourless residue was soluble in hot 2% sodium hydroxide solution (40 c.c.) with a yellow colour. The hot alkaline solution was filtered, cooled and saturated with carbon dioxide, whereupon a colourless, partly crystalline material, m. p. 235—237°, was precipitated (yield, 92 mg.). Ether-extraction of the filtrate gave no further product, and acidification with hydrochloric acid produced no precipitate.



A, Flavonol (VI). *B, Flavonol* (V). *C, Xanthoxyletin.*

The material insoluble in sodium hydroxide solution was boiled successively with water (30 c.c. and 100 c.c.), containing a few drops of 10% sodium hydroxide solution, and filtered. The yellow residue (44 mg.) became colourless on acidification and, after crystallisation from aqueous dioxan, afforded meliternatin. The yellow alkaline solutions were combined and saturated with carbon dioxide. The colourless crystalline precipitate (50 mg.; m. p. 233—235°) was combined with the first product and, after three crystallisations from alcohol, the first with charcoal, colourless, hexagonal plates were obtained, having m. p. 243—244·5°, undepressed by a synthetic sample of 6-hydroxy-3 : 5 : 7-trimethoxy-3′ : 4′-methylenedioxyflavone (Part V, *loc. cit.*) of the same crystalline form and of m. p. 244·5—246°.

The acetate, prepared as for the synthetic specimen (Part V), crystallised from dioxan in colourless, rhombic plates, m. p. and mixed m. p. with the synthetic acetate, 246—247°.

Demethylation of Quercetin Pentamethyl Ether.—(a) *With aluminium chloride.* Quercetin pentamethyl ether, treated similarly to meliternatin, afforded a product crystallising from alcohol in long, pale-yellow, flat needles, m. p. 197—198°, showing a strong fluorescence in concentrated sulphuric acid and giving a brown colour with ferric chloride solution. Kostanecki, Lampe, and Tambor (*Ber.*, 1904, **37**, 1404) record m. p. 197—198° for quercetin 5 : 7 : 3′ : 4′-tetramethyl ether.

(b) *By heating the hydrochloride.* The hydrochloride of quercetin pentamethyl ether was formed by dissolving the ether (100 mg.) in boiling hydrochloric acid (4 c.c.) and acetic acid (1 c.c.) and

crystallisation. The yellow needles, which separated in sheaf-like aggregates, were filtered on a sintered-glass funnel and washed with concentrated hydrochloric acid. This material, while being stirred in an open tube, was heated in an oil-bath up to 160°. Gas was liberated at *ca.* 110—120° and reaction was complete at 160°. The product partly crystallised on cooling, and completely from hot alcoholic solution in fine, pale yellow needles, m. p. and mixed m. p. with quercetin 3 : 7 : 3′ : 4′-tetramethyl ether, 159°. In alcoholic solution it gives a brown colour with ferric chloride solution.

Identification of "Compound E" with Xanthoxyletin.—"Compound E" (Part I, *loc. cit.*), m. p. 133·5—134°, was undepressed in m. p. on admixture with a sample of xanthoxyletin, m. p. 131·5—135·5°, of the same crystalline form. The absorption spectrum measured in *ca.* M/20,000 alcoholic solution, is shown in the figure.

Bromoxanthoxyletin.—Bromine (18·6 mg., 1 mol.) in chloroform solution (1·5 c.c.) was added dropwise to a solution of xanthoxyletin (30 mg. *ex Melicope ternata*) in the same solvent. Absorption of the bromine was at first instantaneous but decolorisation of the last few drops required some seconds. The yellow resin obtained after removal of the chloroform (the last portion in a vacuum) formed, after two crystallisations from slightly diluted alcohol, colourless, hexagonal plates, m. p. 157·5—158·5° (25 mg.), undepressed by a *bromo*-compound of the same m. p. prepared from authentic xanthoxyletin (Found : C, 53·5; H, 5·3; Br, 21·3. $C_{14}H_{13}O_4Br$ requires C, 53·4; H, 3·9; Br, 23·7%).

We are indebted to the Chemical Society, the Australian and New Zeaand Association for the Advancement of Science, the Royal Society of New Zealand, and the Research Grants Committee of the University of New Zealand for continued grants, and one of us (R. H. L.) for a Research Scholarship.

AUCKLAND UNIVERSITY COLLEGE,
AUCKLAND, NEW ZEALAND.

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694. *Chemistry of New Zealand* Melicope *Species. Part VII.* Some Observations on the Relation between the Constitution of Some Flavonol Derivatives and their Acidity, Basicity, Colours with Ferric Chloride, and Ultra-violet Absorption Spectra.*

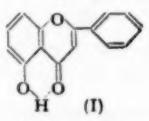
By LINDSAY H. BRIGGS, and R. H. LOCKER.

The relation between the constitution of some related flavonol derivatives and the properties listed in the title is discussed.

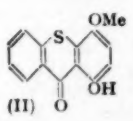
DURING the work described in this series of papers we have recorded the solubility of various flavonols in sodium hydrogen carbonate, sodium carbonate, and sodium hydroxide solutions, and in concentrated sulphuric and hydrochloric acids, their colours with ferric chloride, and their ultra-violet absorption spectra in alcoholic solution. From these observations a number of useful general conclusions may be made.

In Table I are listed the solubilities in concentrated hydrochloric acid and alkalis and the ferric chloride colours of some flavonols, mostly related to this series.

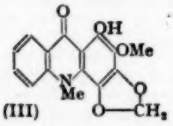
Acidity.—The 5-hydroxyflavonols (9—12) are outstanding by virtue of their insolubility in aqueous alkalis (for further examples see Part VI, preceding paper). 3-Hydroxyflavones also tend to be sparingly soluble (cf. 17 and further examples cited in Part VI). This, however, is not due to their lack of acidity but simply to the fact that their sodium salts are insoluble in water. Ethereal solutions of (9—12) are, however, unaffected by sodium carbonate and



(I)



(II)



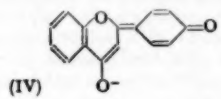
(III)

hydrogen carbonate solutions, thus manifesting their weak acidic properties, as is to be expected because of hydrogen bonding between the 4- or the 5-hydroxyl group and the carbonyl group as in (I).

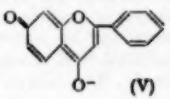
* Part VI, preceding paper.

A similar effect is observed with 1-hydroxy-4-methoxy-10-thioxanthone (II) which contains the same group (Roberts and Smiles, *J.*, 1929, 1322) and with the nor-alkaloids of the melicopine series, *e.g.*, normelicopine (III) (Crow and Price, *Australian J. Sci. Res.*, 1949, **2**, *A*, 255, 282) which are also insoluble in alkalis.

It is possible that the strong acidity of 4′-hydroxyflavonols, *e.g.*, (18), may be due to resonance of its ion with the form (IV), the further stability of the ion enhancing the acidic properties. This is supported by the fact that where hydrogen bonding occurs between the carbonyl group and the 5-hydroxyl group such resonance is no longer possible and the acidic properties are reduced, cf. (6) and (18). A similar resonance (cf. V) is possible with the



(IV)



(V)

7-hydroxyflavonol (15) but its acidity, as shown by its solubility in sodium carbonate solution, is not recorded. However, from a comparison of the compounds (1)—(4) it appears that the 7-hydroxyl group also confers strong acidity on the molecule. Resonance is also possible with

TABLE I.

Properties of flavonols.

No.	Substituents: OH	OMe	OEt	O_2CH_2	Solubility in: Satd. $NaHCO_3$	2N-Na_2CO_3	2N-NaOH	Conc. HCl	Colour in $FeCl_3$
1	3 : 5 : 7 : 3′ : 4′	—	—	—	(+)	+	+	−	+
2	3 : 5 : 3′ : 4′	7	—	—	−	+	+	−	+
3	3 : 5 : 4′	7 : 3′	—	—	−	+	+	−	+
4	5 : 7 : 4′	3 : 3′	—	—	(+)	+	+	−	+
5	5 : 7 : 8	3	—	3′ : 4′	(+)	+	+	−	+
6	5 : 4′	3 : 7 : 3′	—	—	−	−	+	−	+
7	5 : 4′	3 : 7 : 8 : 3′-	—	—	−	−	+	−	+
8	5 : 7	3	—	3′ : 4′	−	−	+	−	+
9*	5	3 : 7 : 3′ : 4′	—	—	−	−	−	−	+
10*	5	3 : 7	—	3′ : 4′	−	−	−	−	+
11†	5	3 : 6 : 7	—	3′ : 4′	−	−	−	−	+
12*	5	3	—	6 : 7 : 3′ : 4′	−	−	−	−	+
13	6	3 : 5 : 7	—	3′ : 4′	−	−	+	+	−
14	6	3 : 5	7	3′ : 4′	−	−	+	+	−
15	7	3 : 5 : 8 : 3′ : 4′	—	—	−	?	+	+	−
16	8	3 : 5 : 7 : 3′ : 4′	—	—	−	?	+	?	+
17	3	5 : 7 : 8 : 3′ : 4′	—	—	−	−	(+)	?	+
18	4′	3 : 5 : 7 : 3′	—	—	−	+	+	+	−

\+ Soluble or, with $FeCl_3$, a brown or green colour. (+) Slightly soluble.
− Insoluble or, with $FeCl_3$, no colour. ? Not recorded.

* These compounds are insoluble in sodium hydroxide but, when dissolved in ether, react with sodium hydroxide solution to form an insoluble sodium salt at the interface. Carbonate and bicarbonate solutions are without action on the ethereal solutions.

† This compound is insoluble in sodium hydroxide solution and practically insoluble in ether. The very dilute solution formed in the latter case produces a yellow colour with sodium hydroxide solution but not with carbonate or bicarbonate solution.

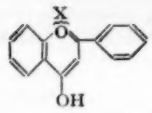
References: 1, Rigaud, *Annalen*, 1854, **90**, 294, and our own observations. 2, Liebermann and Hörmann, *ibid.*, 1879, **196**, 313, and our own observations. 3, Perkin and Geldard, *J.*, 1895, **67**, 498, and our own observations. 4, 6, 18, *J.*, 1950, 864. 5, 8, 10, *J.*, 1949, 2162. 7, *J.*, 1949, 2157; 1950, 864. 9, Our own observations. 11, *J.*, 1950, 2376, 2379. 12, Preceding paper. 13, *J.*, 1950, 2379, and preceding paper. 14, *J.*, 1949, 2157, and preceding paper. 15, Baker, Nodzu, and Robinson, *J.*, 1929, 74. 16, 17, Rao and Seshadri, *Proc. Indian Acad. Sci.*, 1948, **24**, *A*, 375.

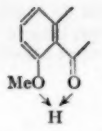
the 5-hydroxyl compounds, but here apparently hydrogen bonding appears to be the dominating factor. The very high acidities of (1) and (4) may be due to the fact that both resonant forms (IV) and (V) are possible, giving still greater stabilisation of the ion. We have observed in the hydroxyanthraquinone series that the polarographic half-wave potentials increase with increasing dissociation constants (forthcoming communication) and in harmony with our observations is that of Geissman *et al.* (*J. Amer. Chem. Soc.*, 1947, **69**, 155) that the polarographic half-wave

potentials, in alkaline solution, of flavonols with free 5-, 7-, and 4'-hydroxyl groups are considerably higher than those in which these positions are methylated.

A hydroxyl group on $C_{(8)}$ apparently does not confer any marked acidity, cf. (13) and (14). A comparison of (5) and (8) shows that one 8-hydroxyl group may lead to increased acidity but it should be noted that 4'-benzyloxy-5 : 7 : 8-trihydroxy-3 : 3'-dimethoxyflavone, like its corresponding 5 : 7-dihydroxy-analogue (Part III, *J.*, 1950, 864), is insoluble in sodium carbonate solution.

Basicity.—All the flavonols obtained during this series of investigations are soluble in concentrated sulphuric acid, giving intensely yellow solutions, and the fully alkylated flavonols are also soluble in concentrated hydrochloric acid, affording similar solutions (cf. *J.*, 1949, 2157, for the preparation of various salts of meliternatin and meliternin, which are decomposed when heated or, instantly, by water). The yellow colour of a solution of meliternatin in concentrated hydrochloric acid disappears on dilution with two volumes of water, and the flavonol is precipitated. The salts of quercetin pentamethyl ether are rather more stable.

(VI) 

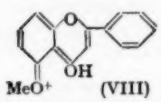
 (VII)

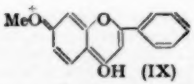
It may be seen from the table that a free 6-, 7-, or 4'-hydroxyl group does not prevent dissolution in hydrochloric acid, but all the flavonols containing a free 5-hydroxyl group are insoluble.

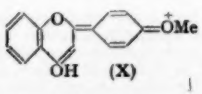
The mechanism of salt formation with γ-pyrone derivatives is still controversial, one view being that they have a benzenoid structure (VI) (cf. Hunter and Partington, *J.*, 1933, 87).

Roberts *et al.* have found (*J.*, 1929, 863, 1322; 1931, 520; 1932, 1792, 1982) that certain methoxyxanthones, methoxy-10-thioxanthones, and $\alpha\alpha'$-dimethoxyanthraquinones dissolve readily in concentrated hydrochloric acid, giving salts which are decomposed by water. They observed that whereas 1-methoxy-10-thioxanthones and 1-methoxyxanthones showed a much greater tendency towards salt formation than other derivatives, 1-hydroxy-4-methoxyxanthone was insoluble in concentrated hydrochloric acid. These properties very closely parallel those of the 5-methoxy- and 5-hydroxy-flavonols of the present investigation.

The effect of the 1-methoxyl group in the salt formation of xanthones was attributed to chelation of the type (VII). Perhaps a more satisfactory explanation for this increased basicity and the more intense colour is that further resonant ions are possible, in the case of flavones, with 5- as well as 7- and 4'-methoxy-derivatives, *e.g.*, the forms (VIII), (IX), and (X) respectively, in addition to those derived from (VI). Since flavonol derivatives with all their phenolic groups free do form salts it appears that the form (VI) must at least be one of the contributing structures.

 (VIII)

 (IX)

 (X)

Further evidence for the intimate association of a neighbouring methoxyl group with salt formation is the fact that heating 1-methoxyxanthones in concentrated hydrochloric acid causes selective demethylation in the 1-position. A similar effect is observed in the *Melicope* alkaloids (Crow and Price, *loc. cit.*). These weakly basic *N*-methylacridones, which are nitrogen analogues of the xanthones, also form mineral-acid salts which are largely hydrolysed in water. Heating the dry hydrochloride, or refluxing it with alcoholic hydrochloric acid, causes demethylation in the 1-position. The resulting nor-alkaloids are even weaker bases than the parent compounds and are also insoluble in alkali (cf. the section on acidity). It appears that with these alkaloids salt formation could be a function of the oxygen rather than of the nitrogen atoms.

Ferric Chloride Colours.—It may be seen from the table that the production of a colour with ferric chloride solution (carried out by the addition of aqueous ferric chloride to an alcoholic solution of the flavone) is a property of 3-, 5-, or 8-hydroxy-compounds (for further

details relating to 3- and 5-hydroxy-compounds see the preceding paper) but not of 6-, 7-, or 4'-hydroxy-derivatives (cf. also, for 6-hydroxyflavones, Seshadri and his co-workers, *Proc. Indian Acad. Sci.*, 1945, **21**, 159; 1945, **22**, 301, 302; 1946, **23**, 274; 1946, **24**, 233, 241; 1947, **26**, 187; for 7-hydroxyflavones, *idem, ibid.*, 1941, **14**, 290; 1945, **22**, 160; 1946, **24**, 377, 457;

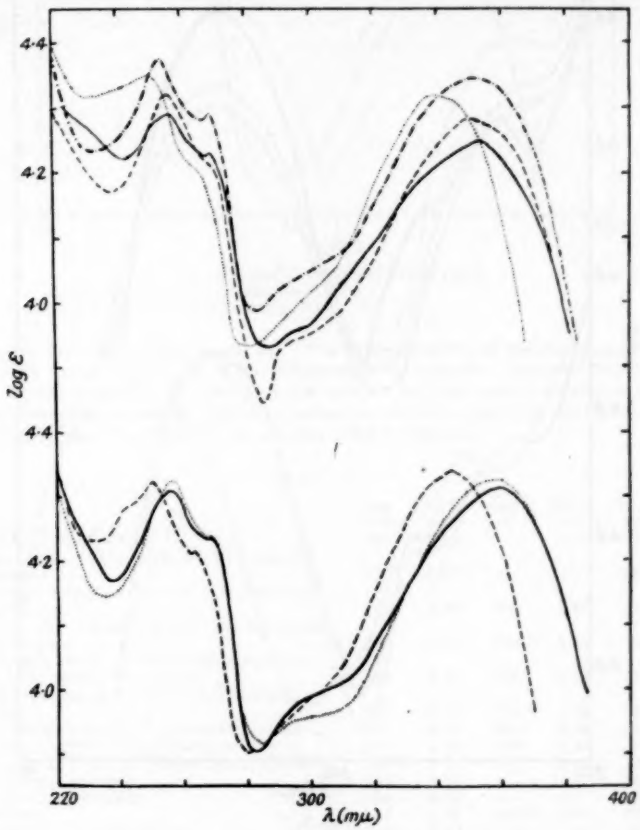


FIG. 1.

FIG. 2.

FIG. 1.

— · — · — · — 5-*Hydroxy*-3 : 7 : 3' : 4'-*tetramethoxyflavone* (A6).
———— 5 : 7-*Dihydroxy*-3-*methoxy*-3' : 4'-*methylenedioxyflavone* (A4).
– – – – – – – – 5-*Hydroxy*-3 : 7-*dimethoxy*-3' : 4'-*methylenedioxyflavone* (A5).
. . . . . 3 : 5 : 7-*Trimethoxy*-3' : 4'-*methylenedioxyflavone* (isohanugin) (A7).

FIG. 2.

. . . . . 5 : 7 : 4'-*Trihydroxy*-3 : 3'-*dimethoxyflavone* (A8).
———— 5 : 4'-*Dihydroxy*-3 : 7 : 3'-*trimethoxyflavone* (A9).
– – – – – – – – 4'-*Hydroxy*-3 : 5 : 7 : 3'-*tetramethoxyflavone* (A10).

1949, **30**, 158; for 4'-hydroxyflavones, *idem, ibid.*, 1946, **24**, 457; *J.*, 1946, 771; 1947, 122). These properties afford valuable structural evidence in support of degradative experiments.

Absorption Spectra.—The ultra-violet absorption spectra of natural and synthetic flavonols obtained in this series of investigations together with a few related compounds are recorded in Figs. 1—5 and in Table II. Unless stated otherwise all spectra were measured in *ca.* M/20,000

alcoholic solutions with a Beckman spectrophotometer, Model D.U. The average accuracy of $\lambda_{max.}$ is *ca.* ±1 mμ, that of log $\varepsilon_{max.}$ *ca.* ±0·01. Some of these results have already been recorded in Part I (*loc. cit.*) and Part II (*J.*, 1949, 2162).*

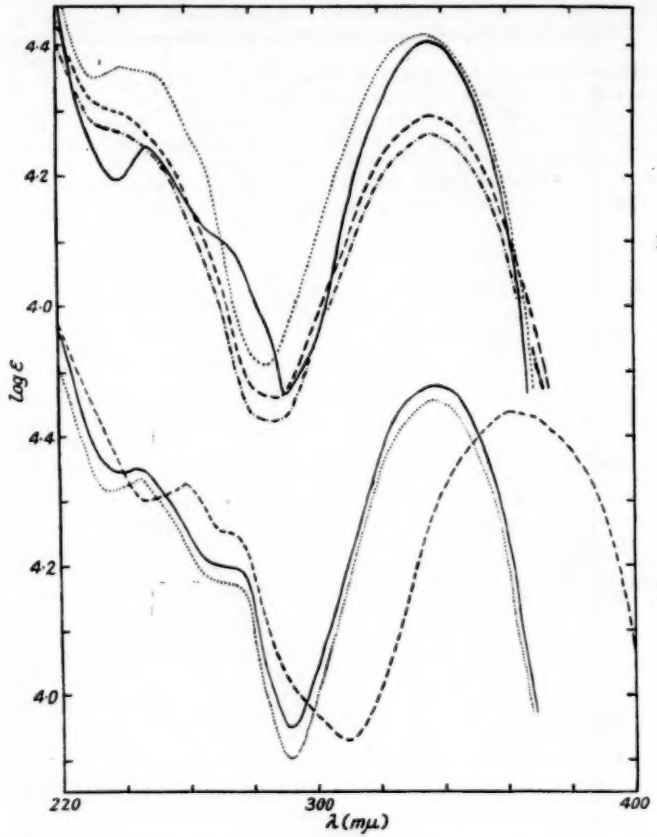


FIG. 3.

FIG. 4.

FIG. 3.

. . . . . *Quercetagetin hexamethyl ether* (A14).
———— *Meliternatin* (A13).
— · — · — · — *Melisimplexin* (*natural*) A11).
– – – – – – *Melisimplexin* (*synthetic*) (A12).

FIG. 4.

– – – – – – *Quercetagetin* (A17).
. . . . . 6-*Hydroxy*-3 : 5 : 7-*trimethoxy*-3′ : 4′-*methylenedioxyflavone* (A15).
———— 7-*Ethoxy*-6-*hydroxy*-3 : 5-*dimethoxy*-3′ : 4′-*methylenedioxyflavone* (A16).

The general pattern of the peaks is fairly constant. In most cases there are two pronounced peaks, at *ca.* 250 (band I) and *ca.* 350 mμ (band III), with a less pronounced peak or point of inflexion at *ca.* 270 mμ (band II).

* The present values are somewhat different from those previously recorded and are the more accurate. Also, owing to an unfortunate interchange of samples, the values already recorded for quercetagetin hexamethyl ether and 5 : 7-dihydroxy-3-methoxy-3′ : 4′-methylenedioxyflavone should be interchanged and slightly amended (as now presented).

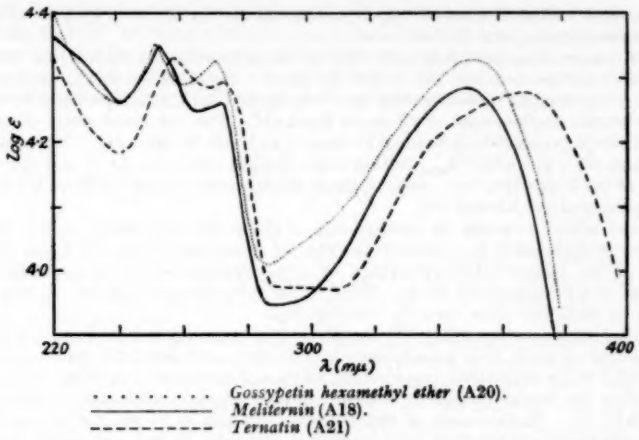


FIG. 5.

(a) *Quercetin derivatives* (Figs. I and II). The measurements of quercetin, quercitrin, and rhamnazin were made by Mr. J. Mills, University of Adelaide, through the courtesy of Professor A. Killen Macbeth, on a Hilger instrument. In these cases no band or inflexion is recorded corresponding to band II (which is present in all other quercetin derivatives) but this is probably due to use of an instrument of lower resolving power.

TABLE II.

		$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε
A1	Quercetin	258	4·32	—	—	375	4·34
A2	Quercitrin (3-rhamnoside)	260	4·35	—	—	352	4·24
A3	Rhamnazin (3 : 5 : 4′-trihydroxy-7 : 3′-dimethoxyflavone)	255	4·37	—	—	375	3·27
A4	5 : 7-Dihydroxy-3-methoxy-3′ : 4′-methylenedioxyflavone	256	4·29	269	4·23	353	4·25
A5	5-Hydroxy-3 : 7-dimethoxy-3′ : 4′-methylenedioxyflavone	255	4·32	269 *	4·21	353	4·28
A6	5-Hydroxy-3 : 7 : 3′ : 4′-tetramethoxyflavone (quercetin tetramethyl ether)	254	4·37	269	4·29	352	4·34
A7	3 : 5 : 7-Trimethoxy-3′ : 4′-methylenedioxyflavone	250	4·35	263 *	4·21	340	4·32
A8	5 : 7 : 4′-Trihydroxy-3 : 3′-dimethoxyflavone	256	4·31	268	4·24	360	4·31
A9	5 : 4′-Dihydroxy-3 : 7 : 3′-trimethoxyflavone	257	4·32	268	4·24	360	4·33
A10	4′-Hydroxy-3 : 5 : 7 : 3′-tetramethoxyflavone	251	4·32	263	4·22	345	4·34
A11	Melisimplexin (natural)	235	4·27	—	—	336	4·26
A12	Melisimplexin (synthetic)	235	4·30	—	—	336	4·29
A13	Meliternatin	248	4·25	269 *	4·11	336	4·41
A14	Quercetagetin hexamethyl ether	240	4·37	—	—	335	4·42
A15	6-Hydroxy-3 : 5 : 7-trimethoxy-3′ : 4′-methylenedioxyflavone	245	4·24	272 *	4·07	337	4·35
A16	7-Ethoxy-6-hydroxy-3 : 5-dimethoxy-3′ : 4′-methylenedioxyflavone	244	4·25	272 *	4·10	337	4·38
A17	Quercetagetin	259	4·27	272 *	4·15	361	4·34
A18	Meliternin (natural)	253	4·35	273	4·26	351	4·29
A19	Meliternin (synthetic)	253	4·36	272	4·27	351	4·29
A20	Gossypetin hexamethyl ether	252	4·34	271	4·33	351	4·33
A21	Ternatin	258	4·33	273	4·29	368	4·28

* Point of inflexion. N.B. The absorption spectrum of melisimplin and 5-hydroxy-3-methoxy-6 : 7 : 3′ : 4′-dimethylenedioxyflavone (preceding paper) could not be included in this survey owing to the insolubility of the substances in alcohol and other suitable solvents.

References: A1, Cf. Grinbaumówna and Marchlewski, *Biochem. Z.*, 1937, **290**, 261. A2, Mayer and Cook, "The Chemistry of Natural Coloring Matters," Reinhold Publ. Corp., 1943, p. 188. A3, *Op. cit.*, p. 190. A4, 5, 7 (*iso*kanugin), 19, *J.*, 1949, 2162. A6, Herzig, *Monatsh.*, 1884, **5**, 72. A8, 9, 10, *J.*, 1950, 864. A11, *J.*, 1950, 2376, 2379. A12, *J.*, 1950, 2379. A13, 14, 18, 20, *J.*, 1949, 2157. A15, Preceding paper. A16, *J.*, 1949, 2157, and preceding paper. A17, Baker, Nodzu, and Robinson, *J.*, 1929, 74. A21, *J.*, 1949, 2157; 1950, 864.

A low-intensity inflexion at *ca.* 300 mμ is a common feature of these derivatives not shared by quercetagetin or gossypetin derivatives.

Band I of quercetin agrees fairly well with the same band of its derivatives, but band III lies considerably further towards the visible spectrum. Substitution at $C_{(3)}$ with a rhamnose unit (A2; this and similar numbers refer to Table II) has little effect on band I but causes a sharp bathochromic displacement of 23 mμ in band III. The combined effect of methylation of the 7- and the 3′-position (A3) is small in band I and zero in band III. Methylation of the 7-position alone does not affect $\lambda_{max.}$ within experimental error (cf. A4–5 and A8–9), whereas methylation of the 4′-position only causes a small displacement (5 mμ) of band III towards the shorter wave-lengths (cf. A7 and 10).

The greatest effect is caused by methylation of the 5-hydroxyl group, which displaces all the bands, particularly band III, towards the shorter wave-lengths (cf. A2–4 and A6–7). The replacement of two vicinal methoxyl groups by a methylenedioxy-group does not affect $\lambda_{max.}$ by more than the experimental error. Band II is remarkably constant at 269 mμ, being affected only by methylation of the 5-hydroxyl group.

(b) *Quercetagetin derivatives* (Figs. III and IV). For these substances band I is present as a peak or an inflexion, band II is an inflexion or is missing, and band III forms a peak of high intensity. With these derivatives replacement of vicinal methoxyl groups by methylenedioxy-groups in either the benzo-nucleus or the side phenyl group considerably changes $\lambda_{max.}$ for band I (cf. A11–14). Methylation of the 6-position causes a 10-mμ bathochromic shift in band I. As expected, substitution of a methoxyl group by an ethoxyl group at $C_{(7)}$ makes practically no difference to the absorption. It is surprising that melisimplexin, intermediate in structure between quercetagetin hexamethyl ether and meliternatin, should have log $\epsilon_{max.}$ for band III *ca.* 0·13 lower than either of these.

(c) *Gossypetin derivatives* (Fig. 5). Since the curves of natural and synthetic meliternin correspond within experimental error only that of the natural product is reproduced. The similarity in the structures of meliternin and gossypetin hexamethyl ether is reflected in their similar absorption curves. The free 5-hydroxyl group in ternatin, as expected, causes a 6-mμ shift in band I towards longer wave-lengths (cf. the quercetin derivatives), band II is unaltered, and the shift of 17 mμ in band III corresponds, within experimental error, with the sum of displacements due to 4′- and 5-hydroxyl groups in the quercetin series.

We are indebted to the Chemical Society, the Royal Society of New Zealand, and the Research Grants Committee of the University of New Zealand for grants, and one of us (R. H. L.) for a Research Scholarship, and to Professor Seshadri for the gift of various flavone derivatives.

AUCKLAND UNIVERSITY COLLEGE,
AUCKLAND, NEW ZEALAND.

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695. *Lanosterol. Part XIII.* Further Experiments on the Constitution of Lanostadienol.*

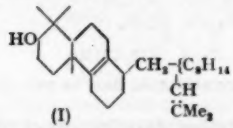
By J. F. CAVALLA, J. F. MCGHIE, and M. K. PRADHAN.

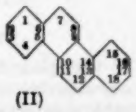
Diketolanostanol and phosphorus pentachloride have been shown to give *iso*lanostenedione which may be further isomerized to give an αβ-unsaturated diketone. The isomerization of lanostenyl acetate has been reinvestigated, and pure *iso*lanostenyl acetate isolated by two routes. Some further examples of bond migration in substituted lanostadienol derivatives are given.

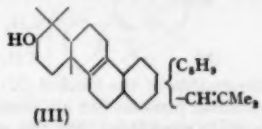
IN Part XII * we summarised the more important facts on the basis of which a partial formula for the tetracyclic triterpenoid alcohol lanostadienol might be suggested, although at the time no actual formula was put forward. Recently the Swiss school have advanced the partial formula (I) for lanostadienol (Voser, Montavon, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893). This formula was suggested by Dr. D. H. R. Barton, in personal discussion with the senior author, considerably before the appearance of the Swiss communication. We have used this partial structure as a background for subsequent investigation and we now submit evidence which supports it.

* Part XII, *J.*, 1951, 2474.

From the dehydrogenation of "lanosterol" with selenium (Schulze, *Z. physiol. Chem.*, **1936, 190,** 52) to 1 : 2 : 8-trimethylphenanthrene the presence of at least three six-membered rings in lanostadienol may be assumed. Furthermore, if we take into account the isolation of a tetramethylchrysene (Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, **1944, 27,** 472), provisionally assigned the 1 : 2 : 7 : 8-structure, we may interpret the ring system of lanostadienol

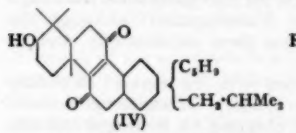

(I)

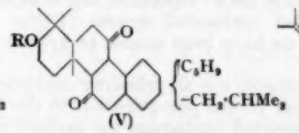

(II)

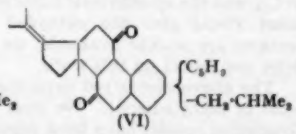

(III)

on the basis of perhydrochrysene (II; numbering as in triterpenes). This may be expanded to (III), by the incorporation of all the known structural features: the inert ethylenic bond is placed at the 9 : 10-bridgehead position, in accordance with formula (I), and we provide confirmatory evidence of this.

Oxidation of either lanostenyl or γ-lanostadienyl acetate is known to give diketolanostenyl acetate (Ruzicka, Rey, and Muhr, *loc. cit.*; Dorée and McGhie, *Nature*, **1944, 153,** 148; Cavalla and McGhie, *J.*, **1951,** 834), which is reduced under fairly mild conditions to diketolanostanyl acetate (Dorée, McGhie, and Kurzer, *J.*, **1948,** 988). On the basis of (III) for lanostadienol these may be formulated as (IV) and (V; R = Ac) respectively. Hydrolysis of (V; R = Ac)


(IV)

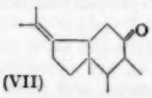

(V)

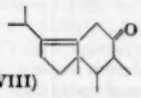

(VI)

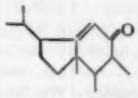
gave hydroxylanostanedione (V; R = H) and this on treatment with phosphorus pentachloride under the conditions resulting in a retropinacolinic change gave either of two products, depending on the reaction conditions. Under the conditions outlined by Dorée, McGhie, and Kurzer (*J.*, **1947,** 1467), for the dehydration of lanostenol and γ-lanostadienol, the only crystalline compound which could be isolated had m. p. 183—184°, considerably depressed on admixture with the starting material. The compound on analysis was found to contain chlorine and was not further investigated. Modification of the reaction conditions gave a substance, m. p. 146—147°, $[\alpha]_D$ +79·4°, which gave analytical figures in good agreement for an *iso*lanostenedione, $C_{30}H_{44}O_2$ (VI), a retropinacolinic change having taken place in its formation from hydroxylanostanedione.

*iso*Lanostenedione was strongly unsaturated to tetranitromethane; lack of high-intensity absorption in the ultra-violet region indicated the absence of a conjugated system, *iso*lanostenedione being correctly represented as (VI).

Treatment of *iso*lanostenedione with hydrochloric acid in acetic acid gave an isomer, m. p. 126°, $[\alpha]_D$ +71°, which unlike its precursor had an absorption maximum at 240 mμ. (log ε 3·98), indicative of the presence of an αβ-unsaturated keto-group. Its formation is readily explained by the partial formula (VII)—(IX), the γδ-ethylenic bond in (VII) passing through the unstable βγ-intermediate (VIII) to give the more stable αβ-unsaturated ketone (IX). These experiments strongly support formula (I) for lanostadienol.

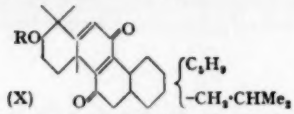

(VII)

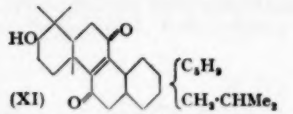

(VIII)


(IX)

In an attempt to avoid the necessity for acid isomerization of the intermediate olefin we turned our attention to dehydrodiketolanostenyl acetate (X; R = Ac) (Voser *et al.*, *loc. cit.*; Cavalla and McGhie, *J.*, **1951,** 744). Voser *et al.* considered that this compound contained an ethylenic bond more than the starting material diketolanostenyl acetate (XI). We have confirmed this in the following manner: Mild reduction of (X; R = Ac) with zinc dust in acetic acid gave a compound, m. p. 177—179°, $[\alpha]_D$ +5·0°, possessing an absorption maximum at 237 mμ. (log ε 4·12); the characteristic maximum of the unsaturated 1 : 4-diketo-grouping ·CO·C:C·CO· at 275 mμ. (log ε 4·2) has disappeared, reduction occurring at the ethylenic bond between the two carbonyl groups. This reduction product was identical with a compound

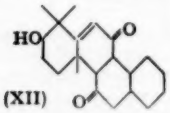
first obtained by Dorée McGhie, and Kurzer (*J.*, 1949, 570) by dehydrogenation of diketolanostanyl acetate with selenium dioxide; consequently the dehydrodiketolanostenyl acetate is correctly represented as (X).

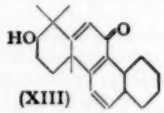

(X)

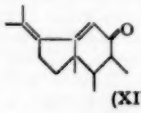

(XI)

Dehydration of the alcohol (X; R = H) with phosphorus pentachloride has, as yet, given no crystalline product (we are continuing our experiments).

We early recognised that the most suitable compounds for further investigations of retropinacolinic change in the lanostadienol group were hydroxylanostenedione (XII) and hydroxylanostatrienone (XIII) (partial formulæ). Both compounds already contain the keto-group


(XII)


(XIII)


(XIV)

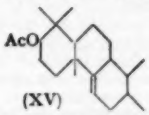
at $C_{(8)}$ and the αβ-ethylenic bond in the 6 : 7-position, and thus in the retropinacolinic rearrangement would give the extended conjugated system (XIV). Unfortunately, although the acetates are readily available, we have been unable to hydrolyse them satisfactorily, and we defer our report on this work.

The above-mentioned experiments are all primarily concerned with the inert 9 : 10-olefinic bond of lanostadienol. We next turned our attention to the isomeric *iso*lanostenyl acetate. Conflicting results have been reported concerning the product obtained by hydrogen chloride isomerization of lanostenol or its acetate. Marker, Wittle, and Mixon (*J. Amer. Chem. Soc.*, 1937, **59**, 1368) reported the values m. p. 147—149° and 162° for *iso*lanostenyl acetate and the alcohol respectively; Wieland and Benend (*Z. physiol. Chem.*, 1942, **274**, 215) reported m. p. 129—130°, $[\alpha]_D$ +46·6°, and m. p. 135—136°, $[\alpha]_D$ +38·0°, respectively; Muhr (Thesis, Zurich, 1945) gave m. p. 132—133°, $[\alpha]_D$ +45·6°, for *iso*lanostenol. Reinvestigation has shown that the compounds described by Wieland and Benend and by Muhr (*locc. cit.*) are mixtures of lanostenyl and *iso*lanostenyl acetates (or alcohols) in varying proportions, but the *iso*lanostenyl acetate described by Marker *et al.* (*loc. cit.*) is pure; when the mixtures obtained by Wieland *et al.* and by Muhr were worked up as laid down by Marker *et al.* (*loc. cit.*) they gave a product, m. p. 146—147°, $[\alpha]_D$ +28·9°, identical with that of Marker *et al.* Marker *et al.* separated their lanostenyl and *iso*lanostenyl acetates by making use of the observation that lanostenyl acetate is more readily attacked by chromic acid under mild conditions: however, these conditions are practically identical with those for the preparation of ketolanostenyl acetate (Marker *et al.*, *loc. cit.*; see also Birchenough and McGhie, *J.*, 1950, 1249), and the melting point of *iso*lanostenyl acetate (147—149°) is very close to that of ketolanostenyl acetate (151—152°). The possibility that the product might be impure ketolanostenyl acetate was ruled out, since analysis gave values agreeing well with the formula $C_{32}H_{54}O_2$. Conclusive evidence of non-identity was that *iso*lanostenyl acetate gave no high-intensity absorption at 255 mμ., characteristic of ketolanostenyl acetate.

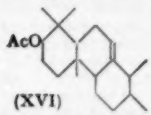
McGhie (Thesis, London, 1947) concluded that the ethylenic bond of *iso*lanostenyl acetate is close to the position occupied in lanostenyl acetate, since *iso*lanostenyl acetate on dehydrogenation with selenium dioxide, and on oxidation with chromic acid, gave the same products (γ-lanostadienyl acetate and diketolanostenyl acetate respectively) as are obtained from lanostenyl acetate. We have confirmed and extended these observations, and have found that either keto- or diketo-lanostenyl acetate may be obtained in the chromic acid oxidation depending on the reaction conditions. Furthermore, oxidation of *iso*lanostenyl acetate with perbenzoic acid afforded both γ-lanostadienyl acetate and ketolanostenyl acetate, the latter presumably arising from the former by further oxidation (see Birchenough and McGhie, *J.*, 1949, 2038; 1950, 1249).

We have also discovered an alternative, more convenient route to *iso*lanostenyl acetate: ketolanostenyl acetate is subjected to Wolff–Kishner reduction in diethylene glycol (Herr, Whitmore, and Schliessler, *J. Amer. Chem. Soc.*, 1945, **67**, 2061); *iso*lanostenyl acetate, m. p. 146—147°, $[\alpha]_D$ +30·0°, is obtained.

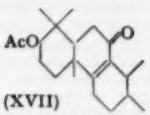
From these experiments it is apparent that bond migration has occurred both in the hydrogen chloride isomerization and in the Wolff–Kishner reduction, and if, as has been postulated, the position of the olefinic bond in *iso*lanostenyl acetate is very close to that in lanostenyl acetate, we can assign two possible partial formulæ (XV and XVI) to *iso*lanostenyl acetate. Formula



(XV)



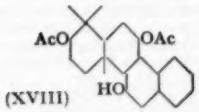
(XVI)



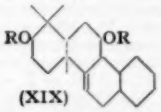
(XVII)

(XV) has already been provisionally assigned to a compound isomeric with *iso*lanostenyl acetate by Voser *et al.* (*loc. cit.*), leaving only (XVI) to be considered; ketolanostenyl acetate may then be represented by (XVII). This implies that the more reactive methylenic group in lanostadieno is at $C_{(8)}$, and we hope later to present confirmatory evidence of this.

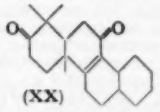
It is of interest that bond migration also occurs in compounds derived from structures analogous to (XV). In Part XI (*J.*, 1951, 834) we reported the dehydration of diacetoxylanostanol (XVIII) to diacetoxylanostene which is best represented as (XIX; R = Ac).



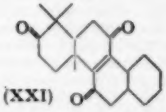
(XVIII)



(XIX)



(XX)



(XXI)

Oxidation of the corresponding diol (XIX; R = H) has afforded a colourless diketone, m. p. 148—149°, $[\alpha]_D$ +17·8°, and a yellow triketone, m. p. 108—109°, $[\alpha]_D$ +16·9°. The former shows an absorption maxima at 254 mμ. (log ε 4·03), indicating the presence of an unsaturated keto-grouping, the ethylenic bond in the 10 : 11-position moving into conjugation with the keto-group at $C_{(8)}$. This diketone is identical with that obtained by the mild oxidation of lanostenol (Wieland and Joost, *Annalen*, 1941, **546**, 103; McGhie, *loc. cit.*), and is to be represented as (XX). The triketone is identical with triketolanostene prepared by the oxidation of diketolanostenol (Ruzicka, Rey, and Muhr, *loc. cit.*; see also McGhie, *loc. cit.*), and is to be represented by the partial formula (XXI).

After these experiments we learnt that Barton, Fawcett, and Thomas had independently reached similar conclusions about the position of the inert ethylenic bond in lanostadienol, and had also carried out some analogous experiments on the constitution of *iso*lanostenyl acetate (see following paper). The results reported in the two papers are in excellent agreement. We thank Dr. D. H. R. Barton for informing us of his results before their general publication.

Experimental.

All m. p.s are uncorrected. Specific rotations were measured in chloroform solution at 20°.* The aluminium oxide used in the chromatographic work was from Messrs. Peter Spence Ltd. (Grade " O "). Analyses are by Drs. Weiler and Strauss, Oxford. Light petroleum refers to the fraction of b. p. 60—80°.

Dehydration of Hydroxylanostanedione with Phosphorus Pentachloride.—Diketolanostanyl acetate on alkaline hydrolysis gave hydroxylanostanedione, m. p. 190—191°, $[\alpha]_D^{20}$ +57·7° (*c*, 2·947) (Dorée, McGhie, and Kurzer, *J.*, 1948, 988, give m. p. 183—184°, $[\alpha]_D$ +26°).

(*a*) Hydroxylanostanedione (1·5 g.) in dry light petroleum (150 ml.), was treated at room temperature with phosphorus pentachloride (1·5 g.) for 2 hours with constant stirring. The mixtare was refluxed for a further hour, then poured into water, the light petroleum layer was washed repeatedly with water, and the solvent removed *in vacuo*, leaving a viscous oil. Passage of this through a column of alumina (10 × 1·3 cm.), in light petroleum (200 ml.) as a carrier, and then elution of the column with light petroleum (500 ml.), followed by removal of the solvent, gave a white solid (0·4 g.). This after two further recrystallizations had m. p. 183—184°, depressed (by 20—30°) on admixture with the starting material, and gave a positive Beilstein test (Found : C, 70·5; H, 9·3%).

(*b*) Reaction was carried out as above, but with half the amount of phosphorus pentachloride. The reaction product, worked up as before, gave a semi-solid material. This was absorbed on alumina from light petroleum (100 ml.) and gave the following fractions on elution : (i) light petroleum (150 ml.), 0·05 g., m. p. 139—144° (from methanol); (ii) light petroleum (150 ml.), 0·09 g., m. p. 140—144° (from methanol); (iii) light petroleum–benzene (4 : 1), 0·4 g., m. p. 140—141° (from methanol); (iv) light petroleum–benzene (1 : 4), 0·15 g., amorphous, m. p. 119—124°. Fractions (i), (ii), and (iii), recrystallized together twice from methanol, gave white felting needles of *isolanostenedione*, m. p. 146—147°, $[\alpha]_D^{20}$ +80·2 (*c*, 2·5) (Found : C, 81·9; H, 10·7. $C_{30}H_{44}O_2$ requires C, 81·8; H, 11·0%).

(*c*) The most satisfactory preparation of *iso*lanostenedione is as follows. A suspension of diketolanostanol (3 g.) and phosphorus pentachloride (1·8 g.) in light petroleum (250 ml.) was stirred for 90

* In previous papers in this series (Part IV onwards), all concentrations were expressed as g. per c.c.

minutes, by which time dissolution was complete. The unchanged pentachloride was decomposed by water (70 ml.), and the product worked up to give a brownish solid. Chromatographic purification on alumina, with light petroleum (150 ml.) as the carrier, followed by elution with light petroleum (3 × 200 ml.), gave the following fractions (each crystallized from methanol) : 0·5 g., m. p. 138—142°; 0·4 g., m. p. 134—139°; 0·5 g., m. p. 112—122°. The first two fractions, recrystallized together from methanol, gave *iso*lanostenedione (0·7 g.), m. p. 145—146°, $[\alpha]_D^{20}$ +79·4 (*c*, 2·2).

Isomerization of iso*Lanostenedione.*—*iso*Lanostenedione (0·9 g.) was refluxed for 14 hours, with concentrated hydrochloric acid (50 ml.) and acetic acid (200 ml.). The solution was poured into water, and worked up in the usual manner, to give a pale brown oil (0·75 g.). This was adsorbed from light petroleum (100 ml.) on a column of alumina (12 × 1·3 cm.). Elution of the column with light petroleum (4 × 200 ml.) gave negligible quantities of oil which on crystallization from methanol gave amorphous products. Elution with light petroleum–benzene (1 : 1; 250 ml.) gave a pale yellow oil (0·55 g.) which crystallized from methanol in hard blades (0·45 g.), m. p. 94—98°. These were purified further by chromatography, to give the $\alpha\beta$-conjugated *isomer* in hard needles, m. p. 126° (0·2 g.), $[\alpha]_D^{20}$ +71·0° (*c*, 2·281) (Found : C, 81·6; H, 10·6. $C_{30}H_{44}O_3$ requires C, 81·8; H, 10·9%). Absorption : Max., 240 mμ. (log ε, 3·98) in alcohol.

Reduction of Dehydrodiketolanostenyl Acetate.—Dehydrodiketolanostenyl acetate (0·3 g.) (Voser, Montavon, Gunthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893; Cavalla and McGhie, *J.*, 1951, 744) in glacial acetic acid (40 ml.) was treated at 80° with zinc dust (approx. 2 g., added in portions). The lemon-yellow solution was rapidly decolorized, and was allowed to remain in contact with the zinc for 30 minutes with occasional shaking. The supernatant liquor was decanted, the residual zinc was washed with warm acetic acid, and the washings were combined with the main solution, and the whole was then diluted with water and extracted with ether. The ethereal solution was washed successively with water, dilute sodium carbonate solution, and water, and the solution dried (Na_2SO_4). Removal of the ether gave a white solid, which after two crystallizations from methanol gave felting white plates of dehydrodiketolanostanyl acetate (0·2 g.), m. p. 177—179°, $[\alpha]_D^{20}$ +5·0° (*c*, 3·0) (Found : C, 77·0; H, 19·1. Calc. for $C_{32}H_{50}O_4$: C, 77·1; H, 10·1%). Absorption : Max., 237 mμ. (log ε, 4·12) in alcohol.

Dehydration of Dehydrohydroxylanostenedione with Phosphorus Pentachloride.—Dehydrohydroxylanostenedione (1 g.) {obtained by hydrolysis of the corresponding acetate; m. p. 135—137°, $[\alpha]_D^{20}$ +82·2° (*c*, 3·2)} and phosphorus pentachloride (0·6 g.) in light petroleum (150 ml.), treated as described in (*b*) and (*c*) for hydroxylanostanedione, did not give a crystalline product, nor did reduction of the oil as described above for the conversion of dehydrodiketolanostanyl acetate.

Isomerization of Lanostenyl Acetate.—A solution of lanostenyl acetate (5 g.) in dry chloroform (80 ml.) was treated under reflux at 0°, for periods varying from 1 to 8 hours. The products so obtained (4·0—4·5 g.) had m. p.s in the range 126—134°. Each was worked up separately by the procedure of Marker, Wittle, and Mixon (*J. Amer. Chem. Soc.*, 1937, **59**, 1368) for β-dihydrolanosteryl acetate (*iso*lanostenyl acetate). Chromatographic purification then afforded identical products of m. p. 146—147°, $[\alpha]_D^{20}$ +30·0° (*c*, 4·0) (Found : C, 81·5; H, 11·6. Calc. for $C_{32}H_{54}O_2$: C, 81·6; H, 11·6%). These products were identical with an authentic specimen of *iso*lanostenyl acetate, m. p. 147—148°, $[\alpha]_D^{20}$ +28·9° (*c*, 3·6), prepared according to Marker *et al.* (*loc. cit.*).

Dehydrogenation of iso*Lanostenyl Acetate with Selenium Dioxide.*—To a solution of *iso*lanostenyl acetate (1 g.) in acetic acid (50 ml.) was added a solution of selenium dioxide (1 g.) in water (0·5 ml.). The mixture was heated under reflux for 3 hours, filtered from selenium, poured into water, and worked up in the usual manner, to give γ-lanostadienyl acetate, m. p. 168—169°, $[\alpha]_D^{20}$ +88·1° (*c*, 3·1) (Found : C, 81·92; H, 11·2%).

Oxidation of iso*Lanostenyl Acetate with Chromic Acid.*—(a) *Formation of ketolanostenyl acetate. iso*Lanostenyl acetate (1 g.) in glacial acetic acid (30 ml.) was treated with chromic acid (0·3 g.) in 90% acetic acid (4 ml.) as described by Marker *et al.* (*loc. cit.*) (see also Birchenough and McGhie, *J.*, 1950, 1249). The product, ketolanostenyl acetate (50—70 mg.), after chromatographic purification and repeated crystallization, had m. p. 151—152° alone or mixed with an authentic specimen, and $[\alpha]_D^{20}$ +20° (*c*, 3·2) Found : C, 79·2; H, 11·0. Calc. for $C_{32}H_{52}O_3$: C, 79·3; H, 10·8%). Absorption : Max., 255 mμ. (log ε, 4·1) in alcohol.

(b) *Formation of diketolanostenyl acetate.* Oxidation of *iso*lanostenyl acetate as described by Cavalla and McGhie, *J.*, 1951, 834, gave pure lanostenedionyl acetate, m. p. 158° alone or in admixture with an authentic specimen, $[\alpha]_D^{20}$ +92·0 (*c*, 2·4).

Perbenzoic Acid Oxidation of iso*Lanostenyl Acetate.*—*iso*Lanostenyl acetate (1 g.) in chloroform (30 ml.) was treated with a chloroform solution of perbenzoic acid (equiv. to 0·08 g. of active oxygen), following the method of Birchenough and McGhie (*J.*, 1949, 2039). The product was worked up in the usual way, dissolved in light petroleum (100 ml.), and adsorbed on a column of alumina (15 × 1·3 cm.). Elution with light petroleum (200 ml.) gave γ-lanostadienyl acetate (0·3 g.), m. p. 167—169°, $[\alpha]_D^{20}$ +87·0° (*c*, 2·61) (Found : C, 81·9; H, 11·0. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%). Absorption : Max., 243 and 252 mμ. (log ε, 4·24 and 4·02 respectively). Further elution with light petroleum–benzene (1 : 1) gave ketolanostenyl acetate (0·1 g.), m. p. 151—152°, $[\alpha]_D^{20}$ +22·0° (*c*, 3·9) (Found : C, 79·2; H, 10·7%). Absorption : Max., 256 mμ. (log ε, 4·1) in alcohol.

Attempted Hydrogenation of iso*Lanostenyl Acetate.*—*iso*Lanostenyl acetate (0·5 g.) and a platinum catalyst (from platinic oxide, 0·3 g.) in glacial acetic acid (50 ml.) were shaken in hydrogen at 60° for 3 hours. No absorption took place, and *iso*lanostenyl acetate, m. p. 146°, $[\alpha]_D^{20}$ +29·0° (*c*, 2·23), was recovered.

Modified Wolff–Kishner Reduction of Ketolanostenyl Acetate.—Ketolanostenyl acetate (1·0 g.) in diethylene glycol (20 ml.) was refluxed with hydrazine hydrate (1 ml.; 100%), for 30 minutes. The mixture was cooled, a solution of sodium (1 g.) in diethylene glycol (10 ml.) was added, and the mixture heated under reflux at 210—220° for 6 hours. The cooled solution was diluted with water, extracted

with ether, and washed with water, and the ethereal solution dried (Na_2SO_4). Removal of the ether gave a light brown solid (0·8 g.). This was acetylated with pyridine (5 ml.) and acetic anhydride (20 ml.) on a steam-bath for 3 hours. The product was worked up in the usual manner, to give the acetate (0·7 g.). This was absorbed on a column of alumina (12 × 1·3 cm.) from light petroleum (100 ml.); elution with light petroleum (300 ml.) gave a product (0·3 g.), m. p. 135—136° (from acetone–methanol); this was impure *iso*lanostenyl acetate, brought by several recrystallizations to m. p. 144—145°, $[\alpha]_D^{20}$ +28·1° (*c*, 2·0). Further elution with light petroleum–benzene (1 : 1) (150 ml.) gave a white solid (0·3 g.) which, recrystallized from benzene–methanol, gave pure *iso*lanostenyl acetate, m. p. 146°, $[\alpha]_D^{20}$ +28·8° (*c*, 3·3) (Found: C, 81·4; H, 11·8. Calc. for $C_{32}H_{54}O_2$: C, 81·6; H, 11·6%). This gave no m. p. depression with authentic *iso*lanostenyl acetate, but gave a depression of 25° with the starting material.

Oxidation of Lanostenediol.—Hydrolysis of diacetoxylanostene (Cavalla and McGhie, *J.*, 1951, 834) gave *lanostenediol* in hard translucent plates, m. p. 213—214°, $[\alpha]_D^{20}$ +94·0° (*c*, 3·1) (Found: C, 81·2; H, 11·4. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%). The diol (1 g.) in glacial acetic acid (100 ml.) was treated at room temperature with a solution of chromic acid (1·5 g.) in 90% acetic acid (15 ml.). The solution was shaken at this temperature for 1 hour, then poured into water, and the excess of oxidant destroyed by sulphurous acid. Working up in the usual manner gave a yellow oil, which was adsorbed on a column of alumina (12 × 1·3 cm.) from light petroleum (100 ml.). Elution with light petroleum–benzene (1 : 1) (500 ml.) gave a white solid (0·5 g.) which crystallized from methanol in felting plates, m. p. 147—149°, $[\alpha]_D^{20}$ +17·8° (*c*, 1·80) (Found: C, 81·9; H, 11·1. Calc. for $C_{30}H_{44}O_2$: C, 81·8; H, 11·6%). Absorption: Max., 254 mμ. (log ε, 4·03). This was identical with the diketolanostene prepared from lanostenol by the method of Wieland and Joost (*Annalen*, 1941 **546** 103). Further elution of the column with benzene (350 ml.) gave a yellow oil (0·3 g.); three recrystallizations from aqueous methanol gave yellow needles of lanostenetrione m. p. 108—109° $[\alpha]_D^{20}$ +169·0° (*c*, 3·7) (Found: C, 79·7; H, 10·5. Calc. for $C_{30}H_{44}O_3$: C, 79·2; H, 10·2%). Absorption: Max., 271 mμ. (log ε, 4·02).

The authors are indebted to Dr. D. H. R. Barton for very helpful discussions and suggestions, to Mr. P. Barker for the specific rotations, and to Professor H. Burton for facilities for the determination of absorption data. One of us (J. F. C.) acknowledges the award of a maintenance grant from the Department of Scientific and Industrial Research.

CHELSEA POLYTECHNIC, MANRESA ROAD, S.W.3. [*Received, May 30th*, 1951.]

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696. *Triterpenoids. Part IV.* Some Observations on the Constitution of Lanostadienol (Lanosterol).*

By D. H. R. BARTON, J. S. FAWCETT, and B. R. THOMAS.

Treatment of diketolanostanol with phosphorus pentachloride leads to the formation of an *iso*lanostenedione, isomerised by acid to an αβ-unsaturated ketone. Similar treatment of triketolanostadienol gives a compound containing the chromophoric system $-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=\overset{|}{C}-CO-\overset{|}{C}=\overset{|}{C}-CO-CO-$, the formulation of which is confirmed by the absorption spectrum of the dicarboxylic acid obtained by fission of the α-diketone grouping with alkaline hydrogen peroxide. The formation of mono-2 : 4-dinitrophenylhydrazones from *iso*lanostenedione and its conjugated isomer distinguishes between the less and more hindered carbonyl groups. These experiments lead to unambiguous partial formulæ for lanostenol and its various oxidation products. Experiments are also described which enable a partial formula to be assigned to *iso*lanostenol.

Dehydrogenation of both "lanosterol" and "lanostene" affords 1 : 2 : 8-trimethylphenanthrene. From this it is concluded that only one of the methyl groups in the latter comes from ring A. On the basis of this and other facts the proven partial formula for lanostenol can be (tentatively) expanded to include two additional angular methyl groups.

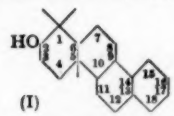
IN the last decade important contributions have been made to our knowledge of the chemistry of lanostadienol (lanosterol), the main triterpenoid component (along with its dihydro-derivative) of the non-saponifiable matter of wool fat. For these advances we are indebted to Ruzicka and his collaborators in Switzerland (*Helv. Chim. Acta*, 1950, **33**, 1893 and earlier papers) and to McGhie and his associates in this country (*J.*, 1951, 834 and earlier papers). It has been established that lanostadienol contains a *sec.*-hydroxyl group (in ring A), flanked by $>CH_2$ and $>CMe_2$ groups and that the more reactive ethylenic linkage is present as the grouping $-CH{:}CMe_2$ in a side chain. Having regard to these facts and to dehydrogenation

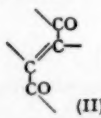
* Part III, *J.*, 1951, 1444.

evidence (Schulze, *Z. physiol. Chem.*, 1936, **238**, 35; Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472) it can be concluded that the carbon skeleton comprises three (rings A, B, and C) and, possibly four (rings A, B, C, and D) six-membered rings. The partial formula (I) summarises these conclusions. In this formula a methyl group is almost certainly attached at $C_{(5)}$, as indicated.

The less reactive ethylenic linkage contained within the tetracyclic nucleus is indicated by the infra-red spectrum of lanostene (Roth and Jeger, *Helv. Chim. Acta*, 1949, **32**, 1620) as fully substituted. Our own examination of the infra-red spectrum of lanostenyl acetate in the 12-μ region confirms this conclusion. In addition, the apparent ultra-violet absorption spectrum in the 195—215-mμ region (see Experimental) corresponds to that of cholest-8(9)-enol rather than of cholest-8(14)-enol and indicates that the double bond must lie between rings B and C or C and D. There is further evidence for this conclusion in the behaviour of lanostenyl acetate on chromic acid oxidation. Under fairly vigorous conditions diketolanostenyl acetate results (Ruzicka, Rey, and Muhr, *loc. cit.*; Dorée and McGhie, *Nature*, 1944, **153**, 148; cf. Wieland and Joost, *Annalen*, 1941, **546**, 103). This compound has a characteristic absorption maximum at about 274 mμ which is indicative of the system $-CO-\overset{|}{C}=\overset{|}{C}-CO-$ in the fully *transoid* arrangement (II) (see Campbell and Harris, *J. Amer. Chem. Soc.*, 1941, **63**, 2721). Other relevant arguments in support of this conclusion are presented by Voser, Montavon, Günthard, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1950, **33**, 1893).

Recently Voser *et al.* (*loc. cit.*) advanced the partial formula (III) for lanostenol. It seemed to us that this was an arbitrary choice and that there was nothing in the published literature to distinguish between the position of the double bond as 9(10) [as in (III)] or as 13(14). Accordingly, our first experiments in this field were directed towards reaching a final distinction between these possible positions for the nuclear double bond. The evidence that we have obtained places the 9(10)-position beyond doubt.


(I)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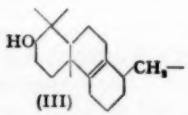
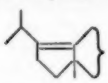
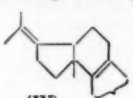
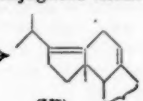
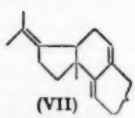

(III)

Reaction of lanostenol with phosphorus pentachloride afforded *iso*lanostadiene (IV) (Dorée, McGhie, and Kurzer, *J.*, 1947, 1467; Ruzicka, Montavon, and Jeger, *Helv. Chim. Acta*, 1948, **31**, 818).* It was hoped that acidic reagents would move the two ethylenic linkages into conjugation, for in comparable *iso*propylidene compounds (Ruzicka *et al.*, *ibid.*, 1945, **28**, 380; 1946, **29**, 210) the double bond moves into the five-membered ring [as in (V)] under such conditions. Indeed, treatment with hydrogen chloride in chloroform gave an isomeric hydrocarbon [probably (VI); see below] but the absorption spectrum showed the presence of only isolated double bonds. Similar isomerisation of *iso*-γ-lanostatriene (VII) (Dorée, McGhie, and Kurzer, *loc. cit.*) likewise failed to give a triply conjugated triene.


(V)


(IV)

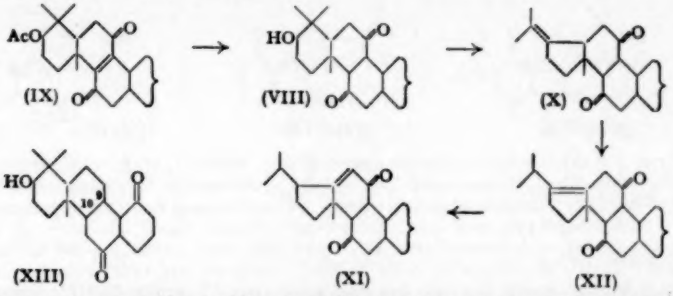

(VI)


(VII)

Greater success attended experiments based on 2-hydroxylanostane-8 : 11-dione (diketolanostanol) (VIII), which is readily prepared (Dorée, McGhie, and Kurzer, *J.*, 1948, 988) by reduction of 8 : 11-diketolanost-9-en-2-yl acetate (diketolanostenyl acetate; see above) (IX), followed by hydrolysis. On treatment with phosphorus pentchloride, (VIII) afforded an *iso*lanostenedione (X) the absorption spectrum of which (Fig. 1) showed the three chromophoric groups to be isolated from each other. Isomerisation of (X) under mild acid conditions gave an isomer (XI) in which the double bond was in conjugation with one of the ketone groups, as shown by the absorption spectrum (Fig. 1). The formation of (XI) is readily intelligible as proceeding through the $\beta\gamma$-unsaturated isomer (XII). The alternative formula (XIII) for diketolanostanol could hardly explain this isomerisation (on the assumption, of course, that no rearrangement of the carbon skeleton occurs) even if there were no methyl groups at

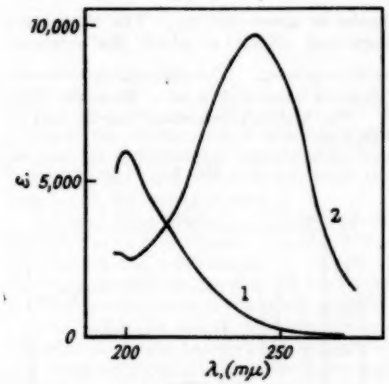
* There seems to be no published proof that *iso*lanostadiene still retains the 9(10)-ethylenic linkage. However, this is very probable, for on similar treatment with phosphorus pentachloride lanostenyl acetate was recovered unchanged almost quantitatively.

$C_{(9)}$ or $C_{(10)}$, for it would proceed through a disecondary ethylenic linkage (at $C_{(7)} : C_{(8)}$) which, itself, would be formed through a carbonium ion produced by the improbable non-Markownikoff addition of a proton to the 6 : 7-double bond.



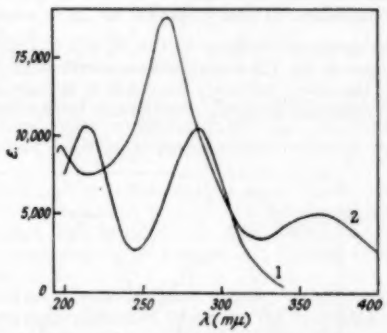
A further, and more rigid, proof for the position of the nuclear double bond at 9(10) was obtained in the following way. Treatment of 2-hydroxylanosta-6 : 9-diene-8 : 11 : 12-trione (lanostadienetrionol) (XIV), itself prepared by hydrolysis of the corresponding acetate (Dorée, McGhie, and Kurzer, *J.*, 1949, 570; Voser *et al.*, *loc. cit.*), with phosphorus pentachloride gave *iso*lanostatrienetrione (XV) in which an extra double bond had clearly been placed in

FIG. 1.



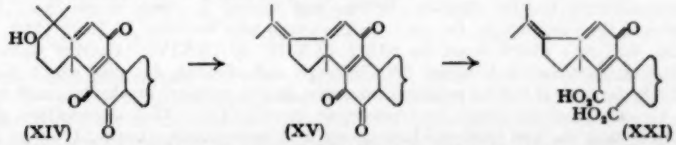
1. iso*Lanostenedione*.
2. *Isomerised* iso*lanostenedione*.

FIG. 2.



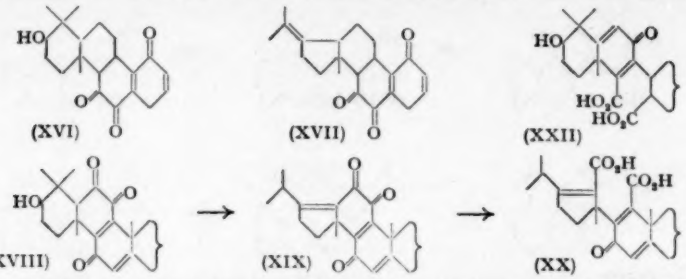
1. 2-*Hydroxylanosta*-6 : 9-*diene*-8 : 11 : 12-*trione*.
2. iso*Lanostatrienetrione*.

conjugation with the original chromophore. This was deduced from the change in absorption spectrum from (XIV) to (XV) (Fig. 2). Obviously if (say) (XVI), with the 13(14)-double bond had been the correct formula for the diene-trione there should have been no change in absorption spectrum on forming the triene-trione, for this would then have been formulated as (XVII). 8 : 11 : 12-Triketolanosta-6 : 9-dien-2-yl acetate, itself, was unchanged by a corresponding treatment with phosphorus pentachloride.



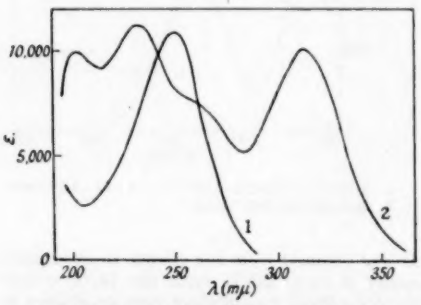
In the above discussion it has been suggested that the diene-trione is represented with the α-diketone grouping in ring C rather than in ring B. This is not altogether unequivocal as it is

formally possible that a diene-trione of formula (XVIII) could give (XIX) on dehydration. The change in chromophoric properties in such a case would not be expected to be so marked as is experimentally observed and in addition it would involve a migration of the double bond



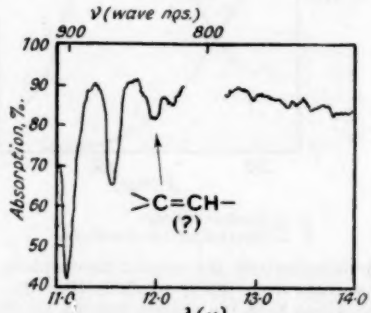
of the *iso*propylidene group into the five-membered ring. Formula (XVIII) was definitely excluded, however, by the following evidence. Oxidation of the diene-trione acetate by alkaline hydrogen peroxide gave a hydroxy-keto-dicarboxylic acid (Cavalla and McGhie, *J.*, 1951, 744) which must contain the chromophoric system $-\overset{|}{C}=\overset{|}{C}-CO-\overset{|}{C}=\overset{|}{C}-CO_2H$. In agreement, it absorbed at 249 mμ (Fig. 3). Similar oxidation of the triene-trione gave a keto-dicarboxylic acid. If the diene-trione had the formula (XVIII) and the triene-trione had formula (XIX), then this dicarboxylic acid (XX) would have (*a*) the same chromophoric system absorbing at 249 mμ. and (*b*) the system $-\overset{|}{C}=\overset{|}{C}-CO_2H$ which absorbs at about 220 mμ. The alternative formulation of the precursor as (XV) would give an acid (XXI) in which the extended chromophoric system $-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=\overset{|}{C}-CO-\overset{|}{C}=\overset{|}{C}-CO_2H$ would be present. The absorption spectrum observed for the trienone-dicarboxylic acid (Fig. 3) shows a band at 311 mμ. Formula (XX) is, therefore, definitely excluded in favour of (XXI). The hydroxy-keto-dicarboxylic acid of Cavalla and McGhie (*loc. cit.*) must be represented by (XXII).

FIG. 3.



1. *Dicarboxylic acid of Cavalla and McGhie.*
2. iso*Lanostatrienetrione oxidation product.*

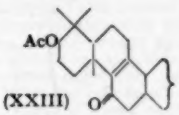
FIG. 4.

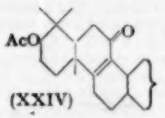


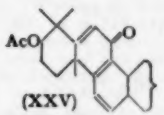
Infra-red spectrum of isolanostenyl acetate.

When lanostenyl acetate is oxidised by chromic acid under controlled conditions it affords a monoketolanostenyl acetate (Marker, Wittle, and Mixon, *J. Amer. Chem. Soc.*, 1937, **59**, 1368; Ruzicka, Rey, and Muhr, *loc. cit.*; Birchenough and McGhie, *J.*, 1950, 1249; Cavalla and McGhie, *loc. cit.*) which must be either (XXIII) or (XXIV). Further oxidation by selenium dioxide furnishes a trienone (Birchenough and McGhie, *loc. cit.*) which must have formula (XXV) because it can be oxidised smoothly (as the acetate) by chromic acid to (XIV). Therefore, the monoketone must be represented by (XXIV). This observation does *not*, however, prove that the less hindered keto-group in 2-hydroxylanostane-8 : 11-dione (VIII) is at $C_{(8)}$ rather than at $C_{(11)}$. *Proof* that it was at $C_{(8)}$ was obtained in the following way. The isolanostenedione (X) afforded, without difficulty, a mono-2 : 4-dinitrophenylhydrazone ($\lambda_{max.}$

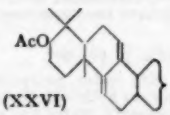
368 mμ in chloroform) in which the double bond was not in conjugation with the hydrazone residue. The isomeric αβ-unsaturated ketone (XI), however, gave a 2 : 4-dinitrophenylhydrazone ($\lambda_{max.}$ 389 mμ in chloroform) in which the double bond *was* in conjugation with the hydrazone residue.

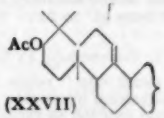

(XXIII)

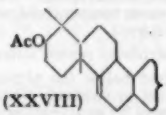

(XXIV)


(XXV)

When lanostenyl acetate is treated with hydrogen chloride in chloroform it is isomerised to an equilibrium mixture of *iso*lanostenyl acetate and (presumably) lanostenyl acetate from which the former compound can be isolated, albeit with some difficulty (Marker, Wittle, and Mixon, *loc. cit.*; McGhie, Thesis, London, 1947; cf. Ruzicka, Rey, and Muhr, *loc. cit.*; Wieland and Benend, *Z. physiol. Chem.*, 1942, **274**, 215). We were interested in this *iso*-compound for it could, conceivably, have had the double bond at 9(14), in which case a methyl group could not have been attached at $C_{(14)}$. However the infra-red spectrum (Fig. 4) indicated that it was triply substituted. On treatment with perbenzoic acid *iso*lanostenyl acetate gave several products. The most important of these was γ-lanostadienyl acetate (dihydroagnosteryl acetate), which must now be formulated as lanosta-8 : 10-dien-2-yl acetate (XXVI). The formation of (XXVI) can best be explained if *iso*lanostenyl acetate is lanost-8-enyl (XXVII) or lanost-10-enyl (XXVIII) acetate. The former of these formulæ was shown to be correct by the characterisation of *iso*lanostenol as the Wolff–Kishner reduction product of (XXIV).


(XXVI)

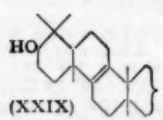

(XXVII)

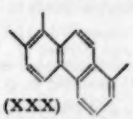

(XXVIII)

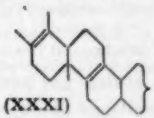
In the latter reaction the double bond shifts from its original position. From its method of preparation *iso*lanostenyl acetate must have the more stable configuration at $C_{(10)}$. Formula (XXVIII) has been correctly assigned to a lanostenyl acetate isomer prepared recently by Voser *et al.* (*loc. cit.*).

The two other products of the action of perbenzoic acid on *iso*lanostenyl acetate which were identified were 8-ketolanost-9-en-2-yl acetate (XXIV), presumably formed by the action of the per-acid on the γ-lanostadienyl acetate (Birchenough and McGhie, *J.*, 1949, 2038), and a saturated ketone which must be formulated as 8-ketolanostan-2-yl acetate. It differed from the 11-ketolanostanon-2-yl acetate of Voser *et al.* (*loc. cit.*).

The failure to obtain evidence for a double-bond isomer at 9(14), which, being tetrasubstituted, would be expected to be favoured thermodynamically [compare the 7(8)-, 8(9)-, and 8(14)-positions in the steroid nucleus], and the failure to extend the unsaturation or substitution beyond the systems represented in (XIV) and (XXV), can be *tentatively* explained by placing methyl groups at $C_{(13)}$ and $C_{(14)}$ as in the lanostenol formula (XXIX). Against such a formulation seemed to be the dehydrogenation evidence. The main dehydrogenation product of lanostadienol was identified by Schulze (*loc. cit.*) as 1 : 2 : 8-trimethylphenanthrene (XXX). This could be interpreted (cf. Voser *et al.*, *loc. cit.*) as arising from a rearrangement in ring A in the sense of (XXXI) giving (XXX). In the particular case of lanostadienol it has now been


(XXIX)


(XXX)

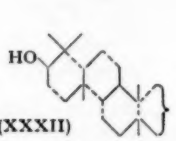

(XXXI)

shown that dehydrogenation of both "lanosterol" itself and of "lanostene" affords 1 : 2 : 8(1 : 7 : 8)-trimethylphenanthrene the yield being superior in the *latter* case. It is very improbable therefore that this phenanthrene can arise by rearrangement of ring A. Thus the dehydrogenation evidence can be reconciled with formula (XXIX) without difficulty.

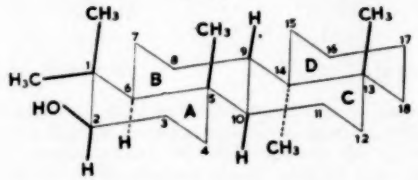
It remains to be pointed out that the part formula (XXIX) obeys the isoprene rule [see (XXXII)]. The differing degrees of steric hindrance of the ketonic groups, in 8 : 11-diketo-

lanostan-2-ol (VIII) could be explained by the stereochemistry shown for lanostanol in Fig. 5. The keto-group at $C_{(11)}$ would then correspond to $C_{(11)}$ in the steroid series (hindrance by *two* polar type C–CH_3 bonds) whilst that at $C_{(8)}$ would correspond to $C_{(4)}$ or $C_{(6)}$ in the steroid series (hindrance by *one* polar type C–CH_3 bond).*

FIG. 5.



(XXXII)



After the experiments described above had been concluded, we learnt that Cavalla, McGhie, and Pradhan had independently reached similar conclusions as to the position of the inert double bond in lanostadienol and had also carried out some analogous experiments on the constitution of *iso*lanostenyl acetate (see preceding paper). The results reported in the two papers are in excellent agreement. We thank Dr. J. F. McGhie for his courtesy in informing us of his results before their general publication.

EXPERIMENTAL.

M. p.s are uncorrected. Unless specified to the contrary rotations were determined in chloroform solution at room temperature, which varied from 15° to 25°. Values of $[\alpha]_D$ have been approximated to the nearest degree.

Light petroleum refers, unless specified to the contary, to the fraction of b. p. 40—60°.

In the test below the phrase " in the usual way " refers to dilution with water, extraction with ether, washing successively with aqueous potassium hydroxide solution, aqueous hydrochloric acid, and water, followed by evaporation of the ethereal solution *in vacuo*. Where necessary, water was removed from the residue by azeotropic distillation *in vacuo* with benzene as entrainer.

Alkaline hydrolyses were effected by using several equivalents of potassium hydroxide and refluxing the reactants for 30—60 minutes in methanolic, ethanolic, or dioxan–methanolic solution, depending on the solubility requirements of the ester.

Ultra-violet absorption spectra were, unless specified to the contrary, measured in ethanol solution, with a Unicam S.P. 500 Spectrophotometer.

Infra-red absorption spectra were kindly determined, in chloroform solution, by Dr. Hans Heymann (Harvard University) using a Baird Associates self-recording double-beam instrument.

Isomerisation of iso*Lanostadiene.*—*iso*Lanostadiene (530 mg.) (Dorée, McGhie, and Kurzer, *J.*, 1947, 1467; Ruzicka, Montavon, and Jeger, *Helv. Chim. Acta*, 1948, **31**, 818) in chloroform (20 ml.) at 0° was treated with a vigorous stream of dry hydrogen chloride for 20 minutes. Removal of the chloroform and dissolved hydrogen chloride *in vacuo* and recrystallisation of the residue from chloroform–methanol afforded an isomeric *hydrocarbon*, m. p. 71°, $[\alpha]_D$ +94° (*c*, 0·83), $\lambda_{max.}$ 201 mμ ($\varepsilon_{max.}$ 10,000) (*c*, 0·0046) (Found: C, 87·8; H, 12·5. $C_{30}H_{50}$ requires C, 87·8; H, 12·2%). When lanostenyl acetate was treated with phosphorus pentachloride under the conditions employed in the preparation of the *iso*lanostadiene, it was recovered unchanged in almost quantitative yield. Isomerisation of the nuclear double bond very probably does not, therefore, occur in the preparation of the latter hydrocarbon.

iso-γ-Lanostatriene, m. p. 135—136°, $[\alpha]_D$ +38° (*c*, 1·96), $\lambda_{max.}$ 235, 243, and 253 mμ ($\varepsilon_{max.}$ 14,000, 17,000, and 11,000 respectively) (720 mg.) (Dorée, McGhie, and Kurzer, *loc. cit.*), was treated similarly with dry hydrogen chloride. Working up as before gave a crude product (from chloroform–methanol), m. p. 75—80°, whose absorption spectrum was similar to that of the starting material. There was no indication of a band corresponding to three double bonds in conjugation.

Dehydration of 2-Hydroxylanostane-8:11-dione.—8:11-Diketolanostan-2-yl acetate was prepared according to the directions of Dorée, McGhie, and Kurzer (*J.*, 1948, 988). Alkaline hydrolysis furnished 2-hydroxylanostane-8:11-dione which, recrystallised from methanol, had m. p. 184—187°, $[\alpha]_D$ +58° (*c*, 1·66). Dorée, McGhie, and Kurzer (*loc. cit.*) recorded m. p. 183—184°, $[\alpha]_D$ +26°, for this compound.

2-Hydroxylanostane-8:11-dione (500 mg.) and phosphorus pentachloride (500 mg.) were suspended in light petroleum of b. p. 60—80° (20 ml.) and left at 0° for 1 hour with occasional agitation. The reaction product, after being worked up in the usual way, was chromatographed over alumina (Birlec). Elution with 1:5 benzene–light petroleum and recrystallisation from methanol furnished *iso-lanostenedione* (X), m. p. 145—146°, $[\alpha]_D$ +76° (*c*, 1·84) (Found: C, 82·0; H, 10·9. $C_{30}H_{48}O_2$ requires

* In Fig. 5 we have *arbitrarily* assumed that rings A and B are *trans*. The differng degrees of steric hindrance for ketonic groups at $C_{(8)}$ and $C_{(11)}$ can equally well be explained in the same way if rings A and B are *cis*. At present we have no preference for either *cis*- or *trans*-fusion of these rings.

C, 81·75; H, 11·0%). The 2 : 4-dinitrophenylhydrazone was obtained on refluxing the reactants for 15 minutes. Purified by chromatography and recrystallisation from chloroform-methanol it had m. p. 215—220°, $\lambda_{max.}$ 368 mμ ($\varepsilon_{max.}$ 20,000) (in chloroform) (Found : N, 9·4. $C_{38}H_{52}O_5N_4$ requires N, 9·05%).

Isomerisation of iso*Lanostenedione.*—*iso*Lanostenedione (200 mg.) was heated under reflux with acetic acid (20 ml.) and concentrated hydrochloric acid (10 ml.) for 12 hours. Working up in the usual way and crystallisation from methanol afforded the *αβ*-unsaturated *isomer* (XI), m. p. 129—130°, $\lambda_{max.}$ 241 mμ ($\varepsilon_{max.}$ 9500) (Found : C, 81·2; H, 10·9%). The 2 : 4-*dinitrophenylhydrazone* (prepared as for *iso*lanostenedione, see above) purified by chromatography over alumina (Birlec) and recrystallisation from chloroform–methanol, had m. p. 233°, $\lambda_{max.}$ 389 mμ ($\varepsilon_{max.}$ 29,000) (in chloroform) (Found : N, 10·0%). When the isomerisation was carried out in dioxan, with refluxing for only 4 hours, a mixture resulted. This was partly resolved on chromatography, the more easily eluted fractions furnishing, after crystallisation from ethanol, colourless plates, m. p. 142—146°, $\lambda_{max.}$ 238 mμ ($\varepsilon_{max.}$ 2800). This substance, which clearly contained about 30% of the *αβ*-unsaturated isomer, gave a 20° depression in m. p. with the starting material and it is possible that it was mainly the *βγ*-unsaturated diketone (XII).

Action of Phosphorus Pentachloride on 2-Hydroxylanosta-6 : 9-diene-8 : 11 : 12-trione.—8 : 11-Diketolanost-9-en-2-yl acetate (5 g.) (Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472; Dorée and McGhie, *Nature*, 1944, **153**, 148) and selenium dioxide (5 g.) were heated under reflux in acetic anhydride (30 ml.) for 3 hours. The precipitated selenium was filtered off and the filtrate diluted with water and worked up in the usual way. Chromatography over alumina afforded 8 : 11 : 12-triketolanosta-6 : 9-dien-2-yl acetate (2·5 g.) which recrystallised from methanol as yellow needles, m. p. 191—192°, $[\alpha]_D$ −68° (*c*, 2·76). This acetate (1·3 g.) was heated under reflux with ethanolic potassium hydroxide (30 ml. of 3%) for 30 minutes and the product worked up in the usual way. Recrystallisation from methanol and then from benzene–light petroleum afforded 2-hydroxylanosta-6 : 9-diene-8 : 11 : 12-trione, m. p. 194—195°, $[\alpha]_D$ −74° (*c*, 2·20) (Found : C, 77·0; H, 10·0. Calc. for $C_{30}H_{44}O_4$: C, 76·9; H, 9·5%). These physical constants are different from those, m. p. 169—172°, $[\alpha]_D$ +37°, reported by Dorée, McGhie, and Kurzer, (*J.*, 1949, 570). In a personal communication Dr. McGhie has kindly informed us that his corrected constants are m. p. 190—191°, $[\alpha]_D$ −71° (*c*, 2·00). The absorption spectrum of the alcohol (see Fig. 2) with $\lambda_{max.}$ 213 and 286 mμ ($\varepsilon_{max.}$ 10,500 in both cases)(*c*, 0·0093) is in good agreement (for the 286-mμ band) with the spectrum for the corresponding acetate (compare Dorée, McGhie, and Kurzer, *loc. cit.*; Voser *et al.*, *Helv. Chim. Acta*, 1950, **33**, 1893). On reacetylation with acetic anhydride and pyridine (0·5 hour at 100°) 8 : 11 : 12-triketolanosta-6 : 9-dien-2-yl acetate was obtained, identical with the starting acetate.

2-Hydroxylanosta-6 : 9-diene-8 : 11 : 12-trione (400 mg.) was dissolved by warming it in 100 ml. of light petroleum (b. p. 60—80°), the solution concentrated *in vacuo* to one-half its volume, then cooled to 0°. Phosphorus pentachloride (1 g.) was added to the suspension, and the mixture set aside at 0° for 5 hours. All the alcohol was by then in solution. After working up in the usual way and chromatography over alumina (Birlec), elution of the bright yellow band with benzene and recrystallisation from methanol gave *iso*lanostatrienetrione (50 mg.), m. p. 154°, $\lambda_{max.}$ 197, 265, and 363 mμ ($\varepsilon_{max.}$ 9,000, 17,500 and 5,000 respectively) (*c*, 0·0040) (Found : C, 80·2; H, 9·3. $C_{30}H_{42}O_3$ requires C, 80·0; H, 9·4%).

8 : 11 : 12-Triketolanosta-6 : 9-dien-2-yl acetate was treated with phosphorus pentachloride under comparable conditions. Working up in the usual way gave back the starting material unchanged.

Action of Alkaline Hydrogen Peroxide on 8 : 11 : 12-Triketolanosta-6 : 9-dien-2-yl Acetate.—This acetate (450 mg.) in dioxan (20 ml.) and methanol (20 ml.) containing potassium hydroxide (300 mg.) was treated at 0° with stirring with "Perhydrol" (5 ml.). After being allowed to warm to room temperature the mixture was poured into water and worked up in the usual way. From the acid fraction there was obtained a product, m. p. 238—239°. This was refluxed with 2% methanolic potassium hydroxide to effect complete hydrolysis and then extracted in the usual way. The resulting hydroxydicarboxylic acid was recrystallised from methanol, and had m. p. 244° (decomp.), $[\alpha]_D$ −46° (*c*, 1·79), $\lambda_{max.}$ 249 mμ ($\varepsilon_{max.}$ 11,000) (Found : C, 71·4; H, 9·25. Calc. for $C_{30}H_{44}O_6$: C, 71·65; H, 9·25%). Cavalla and McGhie (*J.*, 1951, 744) record m. p. 244° (decomp.), $[\alpha]_D$ −58° (*c*, 0·022) in alcohol, $\lambda_{max.}$ 251 mμ ($\varepsilon_{max.}$ 10,700).

Action of Alkaline Hydrogen Peroxide on iso*Lanostatrienetrione.*—A solution of *iso*lanostatrienetrione (120 mg.) in methanolic potassium hydroxide solution (30 ml.; 2%) was treated with "Perhydrol" (3 ml.) at 0° for 3 hours until the colour was almost discharged. After being worked up in the usual way the acidic fraction was rubbed with methanol and water, to give a fine white powder (65 mg.), m. p. 155—170°. This was triturated with ethyl acetate and then recrystallised from the same solvent, to give the *dicarboxylic acid*, m. p. 222° (decomp.), $\lambda_{max.}$ 202, 231, and 312 mμ ($\varepsilon_{max.}$ 10,000, 11,500, and 10,000 respectively) (*c*, 0·0040) (Found : C, 74·1; H, 9·5. $C_{30}H_{44}O_5$ requires C, 74·4; H, 9·2%).

Action of Perbenzoic Acid on Lanost-8-enyl Acetate.—Lanost-8-enyl acetate (500 mg.), m. p. 145—146°, $[\alpha]_D$ +28° (*c*, 1·20), prepared according to the method of Marker, Wittle, and Mixon (*J. Amer. Chem. Soc.*, 1937, **59**, 1368), in chloroform (15 ml.) was treated with 0·74N-perbenzoic acid (8 ml.) in the same solvent. After 4 days the reaction mixture was worked up in the usual way. Chromatography over alumina afforded four compounds : (*a*) Elution by 1 : 1 benzene–light petroleum and recrystallisation from chloroform–methanol gave lanosta-8 : 10-dien-2-yl acetate (dihydroagnosteryl acetate) (105 mg.), m. p. 165—166°, $[\alpha]_D$ +87° (*c*, 2·09), $\lambda_{max.}$ 234, 243, and 252 mμ ($\varepsilon_{max.}$ 15,000, 17,500, and 11,500 respectively) (Found : C, 82·1; H, 11·3. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%), undepressed in m. p. on admixture with an authentic specimen of the same m. p. (*b*) Elution with benzene and recrystallisation from alcohol gave 8-*ketolanostan-2-yl acetate* (30 mg.), m. p. 172°, $[\alpha]_D$ +35° (*c*, 1·81), $\lambda_{max.}$ 288 mμ ($\varepsilon_{max.}$ 40) (Found : C, 79·4; H, 11·2. $C_{32}H_{54}O_3$ requires C, 78·9; H, 11·2%); its 2 : 4-*dinitrophenylhydrazone* had m. p. 244—245°, $\lambda_{max.}$ 365 mμ ($\varepsilon_{max.}$ 21,000) (Found : N, 8·6.

$C_{29}H_{48}O_2N_4$ requires N, 8·4%); this ketone gave no colour with tetranitromethane. (*c*) Further elution with benzene afforded 8-ketolanost-9-en-2-yl acetate which, recrystallised from methanol, had m. p. 155° $[\alpha]_D$ +24° (*c*, 0·83), undepressed in m. p. on admixture with an authentic specimen, m. p. 155—156°. (*d*) Elution with 9 : 1 benzene–methanol and recrystallisation from alcohol furnished a further compound (120 mg.), m. p. 169—170°, $[\alpha]_D$ +17° (*c*, 1·75) (Found: C, 76·8; H, 10·4%). This showed no significant absorption in the ultra-violet region and gave no colour with tetranitromethane. There was a marked depression in m. p. on admixture with the ketone of comparable m. p. referred to above.

After attempted hydrogenation of lanost-8-enyl acetate (100 mg.) in 50 ml. of 10% acetic acid in ether, using a platinum catalyst for 16 hours at room temperature, the product was unchanged starting material, m. p. 146—147°, $[\alpha]_D$ +28° (*c*, 1·20), undepressed in m. p. on admixture therewith.

Dehydrogenation of "Lanostene" with Selenium.—"Lanosterol" (25 g.) (obtained from the non-saponifiable matter of wool fat and consisting of a mixture of lanostenol and lanostadienol) was oxidised by chromium trioxide (4 g.) in suspension in acetic acid (250 ml.) at room temperature for 15 hours, to give "lanostenone" (14 g.). This ketone (30 g.) in acetic acid (1 l.) was reduced with amalgamated zinc (200 g.) and concentrated hydrochloric acid (200 ml.) under reflux for 2 hours. The product was filtered through alumina (Birlec) in light petroleum, to give "lanostene" (22 g.) which was shown to be free from alcohols. "Lanostene" (25 g.) was heated with selenium (20 g.) at 350° for 48 hours and the product extracted with light petroleum and filtered through alumina (Birlec). The resultant oil was chromatographed in light petroleum over alumina, and the solid fractions obtained were combined (500 mg.; m. p. 110—120°), rechromatographed, purified through the picrate, sublimed *in vacuo*, and recrystallised (three times) from alcohol, to give 1 : 2 : 8-trimethylphenanthrene, m. p. 145—146° (Found: C, 92·3; H, 7·4. Calc. for $C_{17}H_{16}$: C, 92·7; H, 7·3%). There was no depression in m. p. on admixture with an authentic specimen of 1 : 2 : 8-trimethylphenanthrene of the same m. p. The absorption spectrum, $\lambda_{max.}$ 211, 223, 262, 282, 293, and 306 mμ, $\varepsilon_{max.}$ 36,500, 19,500, 58,000, 12,500, 12,500, and 15,500 respectively, was also characteristic of 1 : 2 : 8-trimethylphenanthrene. The hydrocarbon was converted into its picrate, m. p. 167—168° (Found: C, 62·6; H, 4·3; N, 9·15. Calc. for $C_{23}H_{19}O_7N_3$: C, 61·4; H, 4·2; N, 9·35%), which gave no depression in m. p. on admixture with an authentic specimen of the same m. p.

"Lanosterol" (5 g.) was heated with selenium (5 g.) at 350—360° for 40 hours. Working up as above gave 20 mg. of phenanthrenoid hydrocarbon, m. p. 115—120°. This was converted into the picrate, m. p. 165—166°, which gave no depression in m. p. with authentic 1 : 2 : 8-trimethylphenanthrene picrate (see above). The yield of the 1 : 2 : 8-trimethylphenanthrene was considerably greater in the dehydrogenation of the "lanostene."

Absorption Spectrum of Lanostenyl Acetate.—In the region 195—215 mμ lanostenyl acetate showed the following apparent absorption spectrum: $\lambda_{max.}$ 200 mμ, $\varepsilon_{max.}$ 4600, ε_{215} 2000 (*c*, 0·0047). According to data kindly provided by Dr. H. B. Henbest (Manchester) this is indicative of a tetrasubstituted double bond as in cholest-8-enol rather than as in cholest-8(14)-enol.

Absorption Spectrum of Lanost-8-enyl Acetate.—In the region 195—215 mμ lanost-8-enyl acetate showed the following apparent absorption spectrum: $\lambda_{max.}$ 200 mμ, $\varepsilon_{max.}$ 3800, ε_{215} 1100. This is quite an acceptable spectrum for a triply substituted double bond (personal communication from Dr. H. B. Henbest).

Preparation of Lanostane (with T. Bruun).—The fundamental hydrocarbon of the lanosterol series, lanostane, was prepared in the following way. Lanost-9-en-2 : 8 : 11-trione (0·7 g.) (Wieland and Joost, *Annalen*, 1941, **546**, 103; McGhie, Thesis, London, 1947) in dioxan (120 ml.) was added to amalgamated zinc wool (from 28·5 g. of zinc and 28 g. of mercuric chloride in 200 ml. of 50% aqueous ethanol), and the mixture refluxed for 3·5 hours. During the first 2 hours 100 ml. of concentrated hydrochloric acid were added portionwise. The reaction product was extracted with light petroleum and chromatographed over alumina. The fraction easily eluted by light petroleum was treated with chromium trioxide (350 mg.) in AnalaR acetic acid (25 ml.) on the water-bath for ½ hour. The reaction product was again filtered through alumina and then crystallised from chloroform–methanol, to give lanostane, m. p. 95—96° (Found: C, 86·9; H, 13·05. Calc. for $C_{30}H_{54}$: C, 86·9; H, 13·1%). For this hydrocarbon Voser *et al.* (*loc. cit.*) reported m. p. 98—99° (corr.).

Wolff–Kishner Reduction of 8-Ketolanost-9-en-2-yl Acetate.—8-Ketolanost-9-en-2-yl acetate (600 mg.) was reduced in three batches, each being heated with 200 mg. of sodium dissolved in 2 ml. of ethanol and 1 ml. of anhydrous hydrazine at 190° for 12 hours. The reaction product, worked up in the usual way, was acetylated and chromatographed over alumina. The more difficultly eluted fractions were enriched in γ-lanosteryl acetate. The more easily eluted fractions were combined and oxidised by chromic acid as for the preparation of *iso*lanostenyl acetate according to the directions of Marker, Wittle, and Mixon (*loc. cit.*). The reaction product, worked up in the usual way and chromatographed over alumina, gave *iso*lanostenyl acetate (lanost-8-en-2-yl acetate), m. p. 145°, $[\alpha]_D$ +32° (*c*, 1·67), undepressed in m. p. on admixture with an authentic specimen of the same m. p. and comparable rotation.

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Birkbeck College, London, W.C.1. [*Received, May 30th*, 1951.]

697. *Organic Reactions in Aqueous Solution at Room Temperature. Part I. The Influence of* pH *on Condensations involving the Linking of Carbon to Nitrogen and of Carbon to Carbon.*

By C. A. C. Haley and P. Maitland.

The object of this series of papers is to broaden the field initiated by Robinson and Schöpf and usually termed "syntheses under physiological (or 'cell-possible') conditions," in relation to both biochemical problems and general organic synthetical methods. Extensive (rather than intensive) investigations have shown that water at room temperature is an effective medium for some very simple condensations involving substances containing the naturally-occurring groups CHO, CO, NH_2, $CO{\cdot}NH_2$, $NH_2{\cdot}C{:}NH$, $CH_2{\cdot}CN$, $CH_2{\cdot}CO$, $CO{\cdot}CH_2{\cdot}CO$, $CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO$ (and $H{\cdot}CO_2H$), leading to well-known examples of Schiff bases, and quinoxaline, diazepine, pyrimidine glyoxaline, pyrrole, and pyridine derivatives. Some failures have suggested that in this type of work a methylene group requires activation from both sides for successful condensation. In two cases of Claisen–Knoevenagel condensations, glycine has been shown to be a useful catalyst. As found by Schöpf in other cases, variation of the pH has striking effects on the yields. Our reaction conditions differed from those used by Robinson and Schöpf in that, while they usually had to isolate their products from solution, we chose water-soluble reactants which produced very insoluble products. A considerable part of the driving force for the reactions is therefore the displacement of equilibria by precipitation. The products in most cases are obtained in reasonable, and sometimes very high, yields after a reaction time of a few days, and are isolated pure direct from the reaction mixture, the usual losses thus being eliminated. Several of the reactions may have preparative value, or may serve for future kinetic investigations. Some of the experimental results support the theory that some reactions, normally considered to be base-catalysed, may also take place under acid-catalysis.

The metabolic routes by which living cells elaborate their multifarious products are only known with certainty in comparatively few instances; but with the introduction into biochemistry of isotopic tracers and organisms with different blocked enzyme systems, and with the general development of spectrographic and chromatographic methods, which offer greater hope of detecting and possibly isolating very labile intermediates, some striking advances in this field of biogenesis may be expected. Although the final proof of any proposed biogenetic origin must always come from the biochemical side, the purely organic chemist has also played a part in trying to elucidate these mechanisms, and contributions to such studies have come from two directions. The first approach, difficult to credit to any single author, concerns the development of the idea that the cell, in addition to its many enzyme-controlled reactions, might produce during the course of its metabolism units which were so reactive that they condensed together without requiring enzymes: the second approach, developed almost entirely by Robinson and closely interlinked with the first, involves architectural analysis of a molecule with a view to detecting the building units.

The earliest ideas regarding non-enzymic cell reactions were first discussed in connection with alkaloid syntheses during 1900—1910 by Pictet, Willstätter, and Winterstein and Trier, and summarised by the last two authors ("Die Alkaloide," Borntraeger, Berlin, 1910, pp. 263—317); but the main theoretical and practical efforts to gain evidence in support of the general theory, by synthesising some natural products under very mild conditions from simple, known (or easily derived) cell units in the absence of enzymes, are associated principally with the work of three authors: Collie during the years 1893—1907 (see Stewart, "Recent Advances in Organic Chemistry," Longmans Green, London, 1927, Vol. I, p. 105) on the conversion of reactive aliphatic compounds (polyketides), which contain repeating $CO{\cdot}CH_2$ groupings, into aromatic compounds; Robinson, with his elegant synthesis of tropinone in aqueous solution at room temperature (*J.*, 1917, **111**, 762), and many outstanding theoretical contributions (*J.*, 1917, **111**, 876; Madrid Lecture, IX Congreso Internacional de Química Pura y Aplicada, 1934; *J.*, 1936, 1079; *J. Roy. Soc. Arts*, 1948, **96**, 795; First International

Congress of Biochemistry, Cambridge, 1949, Report, 1950, p. 32); and Schöpf, with many striking advances in the field of alkaloid syntheses in aqueous solution at 20° or 25° under varying pH conditions, which affect both the yield and the nature of the product (*Angew. Chem.*, 1937, **50**, 779, 797; F.I.A.T. Review of German Science 1939—1946, Preparative Organic Chemistry, Part II, 1948, p. 117; *Chimia*, 1948, **2**, 206). A convincing demonstration both of the soundness of Robinson's original theoretical conceptions of over 30 years ago, and of the importance of Schöpf's controlled pH conditions, has recently been given by Anet, Hughes, and Ritchie (*Nature*, 1949, **163**, 289; 1949, **164**, 501; 1950, **165**, 35), especially in their elegant synthesis of the complex sparteine ring system. The latest contributions to the alkaloid field, which include Woodward's important new concept, have been summarised by Johnson (*Ann. Reports*, 1949, **46**, 195).

In spite of all the above studies and of occasional references in the literature to investigations of this nature, which have come to be known as syntheses under physiological (or " cell-possible ") conditions, we consider that only a beginning in this valuable type of synthesis has been made. The immediate object of the present series of papers is therefore to carry out a broad study of organic reactions in aqueous solution at room temperature, using only mild reagents, simple catalysts, and a wide range of pH conditions, in order to discover what types of reaction are possible under these conditions. It is hoped that this will be of value, first, for the bearing it might possibly have on general problems of biogenesis and on specific attempts at biosynthesis of important cell substances, and, secondly, as a contribution to general synthetic methods. The emphasis has been placed on the discovery of as many types as possible, and the whole study has therefore aimed at being extensive rather than intensive. The model reactions selected are all exceedingly simple, leading to well-known products, but the information gained should enable us to embark later upon more ambitious syntheses. High yields of the products, although very desirable from the preparative aspect and in fact often obtained in the present work, have not been a principal aim from the biogenetic standpoint, because the cell, unlike the chemical models, probably possesses directional control mechanisms which prevent side-reactions: nor has the temperature of the experiments, about 18°, been subject to accurate control, because kinetic investigations were not part of the object.

The main objection to water as a solvent for organic reactions is the sparing solubility of the majority of organic compounds in the solvent, and it is for this reason that it has been comparatively neglected by organic chemists. It must be noted, however, that many organic compounds are loosely stated to be insoluble in water when in fact their solubilities are quite appreciable. In the present series of investigations the solubility at room temperature of the initial reactants has varied from complete miscibility to as low as 0·1%. Solubilities of the order of this low figure, which may still be very much higher than many cell concentrations, were nevertheless found to be experimentally quite practicable.

No limitation will be fixed for pH in these preliminary experiments, and the whole or any suitable part of the range will be examined; but in this connexion the pH values found in living cells are of interest. Concerning the physiologically permissible pH limits, Schöpf and Lehmann (*Annalen*, 1935, **518**, 4) state simply without any supporting evidence that the physiological pH range is 5—9. Small (" pH and Plants," Bailliere, Tindall and Cox, London, 1946) points out the serious difficulties attending the determination of pH in living cells, and the most acceptable method at present is the special indicator method elaborated by Small himself. The normal pH figures for plant sap are 5·0—6·2 but for plants with exceptionally acid metabolism the pH may be as low as 1·7. The figures given for the outer limits of the pH optima for enzymes are instructive. Small (*op. cit.*, p. 78) has compiled a table from various sources which shows that the general range for plant enzymes is 3·5—7·0, but with some extensions on either side—to 2·5 and 10·0. Since direct evidence for the existence of alkaline plant pH's is scanty, it is of interest that Cromwell (*Biochem. J.*, 1950, **46**, 578) has recently recorded a pH of 8·2 in the epidermal glands of the leaves of *Chenopodium vulvaria*. Baldwin (" Dynamic Aspects of Biochemistry," Cambridge Univ. Press, 1947, p. 51), quoting from Haldane's Tables (1930), gives the outer limits for enzymes generally as 1·5—11. Thus two-thirds of the whole pH scale is covered by some supporting evidence from the physiological side. The remaining pH ranges, which so far have never been detected in a living cell, are therefore the very strongly acid and alkaline regions 0—1·5 and 11—14. It is worth mention here that organic reactions found to proceed at pH's higher than 11 may be induced to take place at a lower pH by adopting a device on the lines of that elaborated by Schöpf and Lehmann (*Annalen*, 1932, **497**, 7). These authors have found that the Friedländer quinoline synthesis, which requires a pH of 11—12 for a ketone $R{\cdot}CO{\cdot}CH_3$, can be induced to proceed at pH 7—9,

and thus be brought within the physiological pH range, by using a compound with a more active methylene group, the keto-acid $R{\cdot}CO{\cdot}CH_2{\cdot}CO_2H$, which is decarboxylated during the reaction.

In the present work, the reaction conditions employed differ from those of Robinson and Schöpf, who usually had to extract their products from solution, or precipitate them as derivatives. In our first model experiments, readily accessible reactants have been selected, not necessarily naturally-occurring, but containing reactive groups such as CHO, CO, NH_2, $CO{\cdot}NH_2$, $NH_2{\cdot}C{:}NH$, $CH_2{\cdot}CN$, $CH_2{\cdot}CO$, $CO{\cdot}CH_2{\cdot}CO$, $CO{\cdot}CH_2CH_2{\cdot}CO$ (and $H{\cdot}CO_2H$) which are either found in Nature or can be derived easily from known natural products. The group $CH_2{\cdot}CN$ has been used in two instances as a convenient source of an active methylene group. The CN group itself is of course found in the widely occurring plant cyanophoric glycosides, but only rare instances of naturally occurring compounds containing the $CH_2{\cdot}CN$ group have been reported (Mowry, *Chem. Reviews*, 1948, **42**, 190; Forss, *Nature*, 1951, **167**, 733). All these groups are polar and confer, on the compounds of which they form part, water solubility varying in degree according to the nature of the rest of the molecule. In order to supply what must be a considerable part of the driving force needed to cause interaction of these groups, and also to have a simple means of detecting that it has taken place and of isolating the product, saturated (or strong) aqueous solutions of the polar reactants, either untreated, or with the pH's approximately adjusted, have been so chosen that when allowed to react together at room temperature the polar groups destroy one another and the expected product, a known solid product of high crystallising power and sharp melting point, if formed, is precipitated. In three cases this particular driving force was absent since the product, formed mainly on the acid side and soluble in acid, had to be isolated by making the mixture alkaline. No attempt was made to examine the residual filtrates, but in every case for our own satisfaction the solubility in water of the product was determined in order to obtain some idea of the loss due to this factor. These solubilities are given in the Experimental section only in the few cases where they were appreciable. Since in the majority of cases buffer solutions were used, this figure for pure water could only be applied roughly. It is realised that, under the conditions chosen for these experiments, the equilibrium in a reversible reaction will be shifted in favour of the insoluble product, but all that is desired at present is to show that formation of the product is possible. The living cell may alter the equilibrium by precipitation of the product when a certain concentration is reached, as in the model experiments, or by removing it whilst still in solution by means of a further reaction. The choice of a product with a sharp melting point (when pure) is considered advisable at this stage of the investigations, so that if there is any observed unsteadiness in the melting point of the product obtained it will be an indication that it is due to impurities and not to any inherent instability in the molecule of the product itself. In the present work this rule has been observed in every case except two. The appropriate pH range was obtained by noting the natural pH's of the untreated solutions, or after addition of acid or alkali and, if the results were favourable, a series of more accurate experiments over a wide pH range, using buffer solutions, was carried out in each case, except where the product was too soluble. Difficulties, presumably enhanced by the precipitation of the product, were experienced with buffer capacities, and a large excess of the buffer solution often had to be used with consequent diminished yields of the products.

The products, obtained in good and sometimes very high yield, were isolated by filtration, and after simple washing with water were found in every case but two to be analytically pure, without recrystallisation. They were identified in the usual way by mixed melting points with authentic specimens, confirmed by analysis. The general accuracy of the experiments described in the tables which follow is within 1—2%.

The work is described below in four sections, according to the type of condensation employed, namely, C–N, N–C–N, C–C, and a combination of C–C and C–N. When applicable, the sections are introduced by brief summaries of what is known regarding the biogenetic origin of the system under investigation.

(a) C–N *Condensations leading to Aromatic Schiff Bases, and Quinoxaline, Diazepine, Pyrimidine, and Pyrrole Derivatives.*

Aromatic Schiff Bases.—The first type of reaction selected for study was the interaction between CHO and NH_2 groups to form Schiff bases. In the alkaloid field, in which the attempts to imitate biosynthesis have been so outstandingly successful, Schiff bases have been postulated as intermediates in the reactions involving aldehydo- and amino-groups, although the weight

of evidence obtained appears to favour the previous stage, the hydroxy-amine, as the reactive intermediate (Robinson, *loc. cit.*, 1936; Schöpf and Salzer, *Annalen*, 1940, **544**, 11).

In the reaction between an aldehyde and an amine in general, the hydroxy-amine or Schiff base first formed may subsequently condense with one or other of the reactants, but, when both the aldehyde and the amine are aromatic, the highly crystalline stable Schiff bases are readily formed in high yield, and show no tendency towards the further reaction (Sprung, *Chem. Reviews*, 1940, **26**, 297).

The general conditions for the preparation of Schiff bases normally involve heating alone or in an anhydrous organic solvent, the presence of water usually being regarded as disadvantageous. There are, however, instances where water has been present and the conditions milder (Pyl, *Ber.*, 1927, **60**, 287; Werner, *Sci. Proc. Roy. Dublin Soc.*, 1944, **23**, 214; Cook, Heilbron, and Levy, *J.*, 1947, 1603; Morley and Simpson, *J.*, 1948, 2026; Lutz, *et al.*, *J. Org. Chem.*, 1947, **12**, 763).

In the present paper a representative number of Schiff bases have been prepared from aromatic aldehydes and aromatic amines (including benzylamine) (see Table XX). Several aromatic aldehydes are found free in Nature, but natural occurrence of aromatic amines possessing a free amino-group directly attached to the ring has been reported only in the cases of methyl anthranilate and *p* (and possibly *o*)-aminobenzoic acid. An example from Nature of an aromatic compound containing a free amino-group in the side-chain is tyramine. All the Schiff bases examined are readily formed at room temperature, in yields varying from 70 to 91%, by mixing in equimolecular proportions saturated aqueous solution of the two reactants without interfering with the pH developed. No attempt was made to examine the residual filtrates, which presumably on the large scale could be used again for a further preparation.

It was found that the general reaction could be extended to a reactive ketone: acetylacetone and aniline or *m*-aminophenol in aqueous solution gave the respective pure monoanils in 74% and 84% yield.

All the experiments so far described were very rough and no attempt was made to control the pH developed. Since the reaction commenced so quickly after mixing, no value of the pH during the condensation could be obtained, and only the limits of the probable pH prevailing were recorded. Since the starting materials were so readily accessible, a considerable number of experiments in this one case were performed (see Table XX) in order to establish that the unusual practical conditions were of general application in the field of aromatic Schiff bases, since they may be of preparative value.

The preparation of benzylideneaniline was selected for an accurate study of pH (see Table I). The highest yield (80%) of pure product resulted when precipitation occurred from

TABLE I.

Benzylideneaniline from benzaldehyde (1·06 *g.*) *in buffer solution* (300 *c.c.*) *and aniline* (0·93 *g.*) *in buffer solution* (30 *c.c.*); 2 *days at room temp. M. p.* 51—52°, *pure.*

Buffer	N-HCl–N-NaOAc				0·2N-AcOH–0·2N-NaOAc		0·2N-KH_2PO_4–0·2N-NaOH					
pH, initial and final	1·0 [a]	1·3 [a]	1·6 [a]	3·8 [a]	4·1 [b]	4·9 [b]	5·9	7·0	7·5	7·9	8·2	11·0
Yield, g.	0	0	0	trace	0·79	1·23	1·38	1·45	1·45	1·45	1·34	1·13
Yield, %	0	0	0	trace	44	68	76	80	80	80	74	62
M. p.	←						51—52°					→

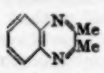
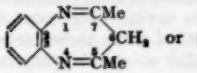
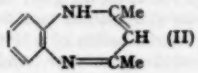
[a] Aniline in 200 c.c. of buffer } to maintain the pH.
[b] „ 140 c.c. „ }

solution at pH 7—7·9, with falling off on either side until on the acid side, at about pH 3·8 and less, no precipitation took place, the most probable explanation being that the equilibrium under these conditions lies on the side of the two reactants.

Quinoxaline.—The general reaction could be extended to include a quinoxaline derivative. *o*-Phenylenediamine and diacetyl were selected as the reactants. Although, as mentioned above, three aromatic compounds containing a free amino-group directly attached to the ring are known in Nature, no naturally occurring aromatic diamine has yet been reported. Diacetyl itself and two of its reduction products play some part in the metabolism of numerous cells (Neuberg, *Adv. Carbohydrate Chem.*, 1949, **4**, 86).

When saturated solutions of the two reactants were mixed at room temperature the solution

deposited directly, without forming an intermediate emulsion, fine needles of pure 2 : 3-dimethylquinoxaline (I) in 93% yield (see Table XX). Gabriel and Sonn (*Ber.*, 1907, **40**, 4850) state that the free base and ketone condense easily in aqueous solution but no details or

(I)   or  (II)

yield are given (they used *o*-phenylenediamine acetate and diacetyl monoxime in warm water). There are many recorded cases, based on Hinsberg's observations (*Annalen*, 1887, **237**, 327) in which *o*-diamines have been condensed in aqueous solution with reactive substances such as glyoxal, phenylglyoxal, pyruvic acid, and certain sugar derivatives, but only occasionally is the reaction carried out at room temperature (*idem*, *ibid.*, 1896, **292**, 245; Ohle, *Ber.*, 1934, **67**, 155; Erlbach and Ohle, *ibid.*, p. 555; see also Lanning and Cohen, *J. Biol. Chem.*, 1951, **189**, 109).

The results of an accurate pH study of the preparation of the quinoxaline (I) are shown

TABLE II.

2 : 3-*Dimethylquinoxaline* (I) *from* o-*phenylenediamine* (1·08 g.) *in buffer solution* (45 *c.c.*) *and diacetyl* (0·86 *g.*) *in buffer* (5 *c.c.*); 1 *day at room temp.* *M. p.* 105—107° (*pure*).

Buffer	N-HCl–N-NaOAc	N-NaOAc–N-AcOH		N-KH_2PO_4–N-NaOH			
pH (initial and final) ...	3·0 *	4·0	5·5	7·1	8·5	9·0	11·6
Yield, g.	0·70	1·28	1·55	1·55	1·50	1·46	1·30
Yield, %	44	81	98	98	95	92	82
M. p.	← 105—107° →						97—103°

* Final pH 1·7, even with 100 c.c. of buffer.

in Table II. Exceptionally high yields (maximum, 98%) of pure product were obtained over the pH range 4·0—9·0. At pH 11·6 the product was impure, owing very probably to self-condensation of the diacetyl (cf. von Pechmann, *Ber.*, 1888, **21**, 1420; von Pechmann and Wedekind, *Ber.*, 1895, **28**, 1846; Diels, Blanchard, and von der Heyden, *Ber.*, 1914, **47**, 2355).

Diazepine.—The reaction between *o*-phenylenediamine and acetylacetone, to give the seven-membered ring compound, 5 : 7-dimethyl-2 : 3-benzo-1 : 4-diazepine (II) (Thiele and Steimmig, *Ber.*, 1907, **40**, 955; Witter, Snyder, and Stotz, *J. Biol. Chem.*, 1948, **176**, 493), was next investigated. Acetylacetone itself has not been reported in Nature, but the β-diketonic grouping occurs occasionally. When saturated aqueous solutions of the two reactants were mixed at room temperature, the pure product crystallised out overnight in 36% yield. Our analyses and molecular-weight determinations support the formula suggested by Thiele and Steimmig.

An accurate pH study is reported in Table III below. Owing to the appreciable solubility

TABLE III.

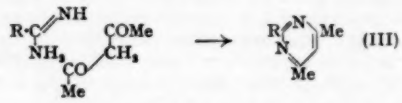
5 : 7-*Dimethyl*-2 : 3-*benzo*-1 : 4-*diazepine* (II) *from* o-*phenylenediamine* (1·08 *g.*) *in water* (10 *c.c.*) (*approx.* pH *attained by addition of* AcOH), *and buffer solution* (25 *c.c.*), *and acetylacetone* (1·0 *g.*) *in buffer* (20 *c.c.*); 2 *hours at room temp.* *M. p.* 131—133° (*pure*).

Buffer	N-AcOH–N-NaOAc		0·2N-KH_2PO_4–0·2N-NaOH			
pH (initial and final)	3·8	4·8	5·8	6·8	7·7	8·2
Yield, g.*	0·79	1·04	0·97	0·85	0·21	0
Yield, %*	46	60	56	49	12	0
M. p.	← 130—132° →		← 131—133° →			

* Anhydrous.

of the product on the acid side the conditions employed here were not the normal. After the reaction had taken place during two hours at the pH indicated, the product was isolated by the addition of excess of dilute aqueous sodium hydroxide. Although there is no condensation above pH 7·7, this treatment might have invalidated the results of the accurate pH study, but in fact a considerable difference in the yields at various pH s was actually observed. Table III shows the maximum yield (56%) of pure product at pH 5·8. At pH values less than 3·8, the deep violet hydrochloride was precipitated.

Pyrimidines.—The evidence for the biological origin of the pyrimidine nucleus in simple pyrimidines (Mitchell and Houlahan, *Fed. Proc.*, 1947, **6**, 506; Heinrich and Wilson, *J. Biol. Chem.*, 1950, **186**, 447; Wright *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 1898) or in purines (Bentley, *Ann. Reports*, 1948, **45**, 250; Schlenk, *Adv. Enzymol.*, 1949, **9**, 460) is so exceedingly slender that no definite conclusions can be made. The most widely used chemical method of synthesis involves condensation of a N–C–N and a three-carbon unit. Since this type of synthesis offers experimental advantages (readily accessible materials and known reference compounds) it was chosen for investigation. From the many possible units used in this method three amidines and a β-diketone were selected.



(III)

The normal experimental conditions for this type of pyrimidine synthesis are condensation under anhydrous conditions with alcoholic sodium ethoxide, usually under reflux but sometimes in the cold. Acid conditions have been used occasionally (Rose and Swain, *J.*, 1945, 689; Curd, Graham, and Rose, *J.*, 1948, 594; Roblin and English, U.S.P. 2,309,739; *Chem. Abs.*, 1943, **37**, 3768). There are, however, a few cases in which the conditions reported were milder and water was present. In Pinner's orginal method (*Ber.*, 1893, **26**, 2122) aqueous potassium carbonate solution was used, but few details and no yields were given. In the special case where a very reactive β-dialdehyde replaces the β-diketone, as in the condensation of sodium nitromalondialdehyde with benzamidine hydrochloride or guanidine carbonate in water at room temperature (Hale and Brill, *J. Amer. Chem. Soc.*, 1912, **34**, 91) the pyrimidines were obtained almost immediately on mixing the solutions of the reactants. As mentioned below in the pyrrole section, sodium nitromalondialdehyde is not suitable for use in a pH study.

The compounds selected for a pH study were 2-amino-4 : 6-dimethyl- (III; R = NH_2), 4 : 6-dimethyl-2-phenyl- (III; R = Ph), and 2 : 4 : 6-trimethyl-pyrimidine (III; R = Me), prepared by condensing acetylacetone with guanidine, benzamidine, and acetamidine respectively. Difficulties were experienced here with buffering action, even when large amounts of the buffer solutions were used. In addition, the appreciable solubility in water of two of the products and the very slow speed of all the condensations made it advisable to work in as concentrated solution as possible. The more approximate method of adding potassium carbonate to the aqueous mixture of acetylacetone and the requisite amidine salt and determining initial and final pH's had therefore to be adopted.

The results for guanidine and benzamidine are given in Tables IV and V. Although both

TABLE IV.

2-*Amino*-4 : 6-*dimethylpyrimidine* (III; R = NH_2) *from guanidine carbonate* (0·90 *g.*), *acetylacetone* (1·0 *g.*) *and* K_2CO_3 (*or* HCl) *in water* (10 *c.c.*); 20 *days at room temp.* *M. p.* 152—154° (*pure*).

K_2CO_3, g.	[b]	0	0·7	2·8
Initial pH	8·5	9·0	9·2	10·0
Final pH	7·3	7·7	8·0	8·6
Yield, g.[a]	0	0·44	0·63	0·76
Yield, %[a]	0	36	51	62
M. p.	←	152—154°		→

[a] Anhydrous. [b] 2 c.c. of N-HCl.

TABLE V.

4 : 6-*Dimethyl*-2-*phenylpyrimidine* (III; R = Ph) *from benzamidine hydrochloride dihydrate* (1·93 *g.*), *acetylacetone* (1·0 *g.*), *and* K_2CO_3 *in water* (10 *c.c.*); 19 *days at room temp.* *M. p.* 81—83° (*pure*).

K_2CO_3, g.	0	0·05	0·3	0·5	0·7	1·0	2·8
Initial pH	4·0	7·5	8·7	8·8	8·9	9·1	9·6[a]
Final pH	4·0	6·5	7·9	8·1	8·2	8·3	8·9
Yield, g.	0	0	0·15	0·34	0·47	0·66	1·17
Yield, %	0	0	8	18	26	36	64
M. p.	←			81—83°			→

[a] At pH >10, benzamidine was hydrolysed to benzamide.

pyrimidines started to come out of solution after 1 day, the necessary duration of the experiments was considerable (19—20 days), especially when compared with the speed of the analogous condensation, under comparable conditions, with a β-ketonic ester (Cook and Reed, *J.*, 1945, 399). The maximum yields of pure products obtained were 62% (2-amino) and 64% (2-phenyl). No details are given regarding the preparation of 2 : 4 : 6-trimethylpyrimidine dihydrate, from acetamidine, except to record that, although examined over a pH range, only under Bowman's conditions (*J.*, 1937, 494), which we found to correspond to pH 9·6, was any product precipitated.

Since the 2-phenyl derivative is very insoluble in water and does not dissolve in acid buffers until pH 1—2, the pH range was in this case extended to pH 4, the natural pH of an aqueous solution of the reactants, but no product was precipitated.

It would thus appear that this type of condensation between an amidine and a β-diketone proceeds only on the alkaline side, with the optimum range at pH 9—10.

Pyrroles.—One of the methods described below in section (d) (method B) should properly be described now as it is an example of a C–N–C condensation. For convenience in having the three pyrrole methods together, however, it has been placed in section (d).

(b) N–C–N *Condensations to give Glyoxaline Derivatives.*

Only two approaches have been made to the biogenesis of the widely occurring glyoxaline nucleus; the first was by Robinson (*locc. cit.*, 1934, 1936); and the second [summarised by Bentley (*loc. cit.*, p. 248) and by Schlenk (*loc. cit.*; see also Heinrich and Wilson, *loc. cit.*)] is supported by biological tracer experiments. The evidence suggests that the glyoxaline ring in purines may be built up from the C–C–N atoms of glycine, a C atom from the carboxyl group of formic or acetic acid, and a N atom from a non-specific nitrogen source. It is not known what the sequence is. If the route required attachment of the nitrogen first to the glycine residue, it might involve a final condensation between a diamino-compound and formic (or acetic) acid. Since formic acid has also been shown to take part with glycine in a metabolic process in a rat (Swanson and Clark, *Ann. Rev. Biochem.*, 1950, **19**, 251; Bentley, *loc. cit.*, p. 243), and since it is so reactive chemically compared with acetic acid, it was selected for our studies.

Benziminazole.—The first reaction chosen for an accurate pH study was the condensation of *o*-phenylenediamine and formic acid to give benziminazole. This condensation is usually carried out under vigorous conditions (*Org. Synth.*, *Coll. Vol.* II, p. 65; Phillips, *J.*, 1928, 2395). Since benziminazoles are readily soluble in mineral acids and in excess of caustic alkalis, they are isolated from strongly acid or alkaline solution by final treatment with ammonia to pH 8·5—9.

The results of an accurate pH study of the preparation of benziminazole are given in Table VI. The product remained in solution during the experiments and, after removal of an

TABLE VI.

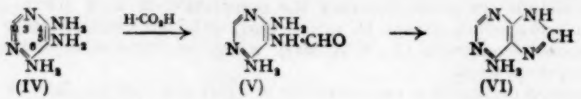
Benziminazole from o-*phenylenediamine* (1·08 *g.*), *formic acid* (90%; 1 *c.c.* ≡ 2 *mols.*), *and buffer solution* (30 *c.c.*); 5 *days at room temp.* *M. p.* 169—171° (*pure*).

Buffer	3N-HCl	N-NaOAc–N-HCl				
pH, initial and final	0·2	0·5	1·8	2·3	2·7	3·3
Yield, g.	0·79	0·98	0·60	0·29	0·08	0
Yield, %	67	83	51	25	7	0
M. p.	←	169—171°				→

impurity described in the Experimental section, was precipitated by adjustment to pH 8·5—9 with ammonia. It will be seen that pure benziminazole is formed under these mild conditions only between pH 0·2 and 2·7, the highest yield (83%) being obtained at pH 0·5.

Adenine (*Attempts*).—The second glyoxaline ring synthesis attempted was the condensation of 4 : 5 : 6-triaminopyrimidine (IV) with formic acid, in the hope of obtaining adenine (VI), under mild conditions. Although in the biosynthesis of purine derivatives some facts have been presented in support of the view that the pyrimidine ring is formed last (Bentley, *loc. cit.*; Schlenk, *loc. cit.*), the evidence is not conclusive as yet. Synthesis of this important purine was first accomplished by Traube (*Annalen*, 1904, **331**, 64; cf. Hoffer, Emil Barell Jubilee Vol., Basle, 1946, p. 428) whose cyclisation procedure involved heating a formamido-derivative at 230°. This method was too vigorous to be employed by Todd *et al.* in the synthesis of purine derivatives of biological importance, and the milder method elaborated consisted of heating the

more reactive thioformamido-derivatives with basic reagents (Baddiley, Lythgoe, McNeil, and Todd, *J.*, 1943, 383; Howard, Lythgoe, and Todd, *J.*, 1945, 560; Kenner and Todd, *J.*, 1946, 852; Andrews, Kenner, and Todd, *J.*, 1949, 2302). In a recent synthesis of theophylline



(IV) (V) (VI)

which involved a final cyclisation of a formamido-compound, the conditions employed were short heating in aqueous sodium hydroxide (Gepner and Kreps, *J. Gen. Chem. Russia*, 1946, **16**, 179; *Chem. Abs.*, 1947, **41**, 96; see also Bobranski and Synowiedski, *J. Amer. Pharm. Assoc., Sci. Edn.*, 1948, **37**, 62).

Although it is well-known that in the pyrimidine (IV) only the amino-group in position 5 shows normal properties (Lythgoe, *Quart. Reviews*, 1949, **3**, 201; for ultra-violet light absorption studies see Marshall and Walker, *J.*, 1951, 1004) it seemed just possible that at some definite pH an amino-group in position 4 or 6, instead of being involved in tautomerism with the adjacent ring-nitrogen atom, might react normally. In experiments, at a buffered pH range, with 4 : 5 : 6-triaminopyrimidine and formic acid in water at room temperature, the product was isolated at the end by bringing the pH to 8·5—9·0 with ammonia. In every case, however, the product, which had an indefinite m. p., gave analytical results for the uncyclised 5-formamido-compound (V) (see Table VII). The product was formed only at pH 0·3—2·8, the highest yield (61%)

TABLE VII.

4 : 6-*Diamino-5-formamidopyrimidine* (V) *from* 4 : 5 : 6-*triaminopyrimidine* (0·31 *g.*), *formic acid* (90%; 0·2 *c.c.*, ≡ *ca.* 2 *mols.*), *and buffer solution* (10 *c.c.*); 4 *days at room temp. M. p.*[a] *ca.* 300—360°.

Buffer	1½N-HCl	N-NaOAc–N-HCl					
pH (initial and final)	0·3	1·1	2·2	2·8	3·0	3·3	3·8
Yield, g.	0·17	0·23	0·17	0·01	0	0	0
Yield, %	45	61	45	3	0	0	0
M. p.[a]	← About 300—360° →						

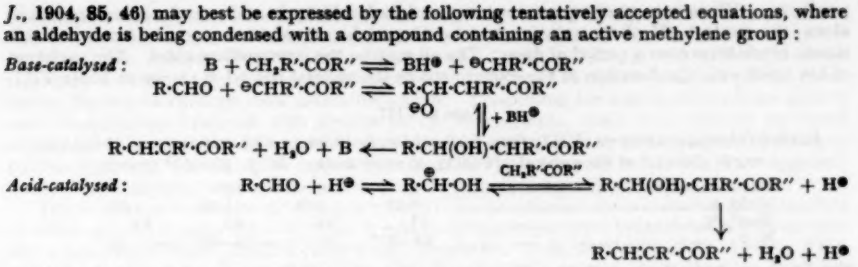
[a] Melting commences at about 300°, followed by slow resolidification and final melting at about 360° (the m. p. of adenine). If plunged into the m. p. apparatus at 360°, the substance melts immediately, resolidifies, and melts again at once.

being obtained at pH 1·1. Since there was a possibility that the synthesis of adenine itself under comparatively mild conditions might proceed in two stages (formylation and cyclisation) necessitating different pH conditions, the formamido-derivative, formed at acid pH and known by its method of isolation to be stable at pH 9, was treated with sodium hydroxide solutions of pH 11, 12, 13, and 14 in the cold, and then adenine searched for by Kossel's test (*Z. physiol. Chem.*, 1888, **12**, 252), but without success. At pH 14 the formyl group was removed, and the original triaminopyrimidine was obtained. In order to prove the constitution of the formamido-derivative it was finally cyclised to adenine at 230° [it has since been made by Cavalieri *et al.*, (*J. Amer. Chem. Soc.*, 1949, **71**, 533) by a vigorous method, and by Clark and Kalckar (*J.*, 1950, 1029) in cold aqueous solution].

(c) C–C *Condensations of the Claisen–Knoevenagel Type* (*also Glycine-catalysed*).

The Claisen and the Knoevenagel reactions, which were originally easily distinguished, are now difficult to define separately. They are at present considered to belong to the larger group of reactions which have been classified until recently as base-catalysed reactions. Modern work on reactions of the Claisen–Knoevenagel type has shown that in certain cases these may be catalysed by either bases or acids (Watson, " Modern Theories of Organic Chemistry," Oxford Univ. Press, 1941, pp. 152—158; *Trans. Faraday Soc.*, 1941, **37**, 707; Hammett, " Physical Organic Chemistry," McGraw-Hill, New York, 1940, pp. 343—348; Dewar, " The Electronic Theory of Organic Chemistry," Oxford Univ. Press, 1949, pp. 107, 123—125). The essential features of both of these reactions, which were first recognised by Lapworth nearly 50 years ago (*J.*, 1901, **79**, 1269; Lapworth and Hann, *J.*, 1902, **81**, 1508; Hann and Lapworth,

J., 1904, **85**, 46) may best be expressed by the following tentatively accepted equations, where an aldehyde is being condensed with a compound containing an active methylene group :



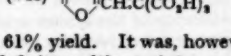
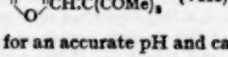
In the first case the reaction starts by the base pulling off a proton, and in the second by the aldehydonium cation pushing off a proton, from the activated methylene group (cf. Swain, *J. Amer. Chem. Soc.*, 1950, **72**, 4578, who has suggested that for polar reactions in water a concerted push–pull mechanism may be operating). Both mechanisms postulate an intermediate aldol stage, and in some cases this has been isolated. From the equations it can be inferred that the more activated the methylene group, the weaker will be the basic or acidic catalyst required to cause the removal of the essential proton, and the milder the conditions necessary for the reaction to take place. With a suitable choice of reactants these condensations might be induced to proceed under very mild conditions indeed in aqueous solution; and with a very reactive methylene compound it is possible that it would be sufficiently ionised in water to proceed without a catalyst—unless the solvent itself is considered to be the catalyst.

There are occasional references, spread over many years, to the Claisen–Knoevenagel type of reaction being carried out in aqueous solution in the cold in presence of alkali, but only recently has the importance of pH control been stressed (Schöpf and Thierfelder, *Annalen*, 1935, **518**, 127; D.R.-P. 702,894, 703,952; Hinz, Meyer, and Schücking, *Ber.*, 1943, **76**,676; Schechter, Green, and LaForge, *J. Amer. Chem. Soc.*, 1949, **71**, 1517, 3165; cf. Schöpf, *ibid.*, 1950, **72**, 2816). The most systematic study is that of Schöpf and Thierfelder, who examined the condensation between aldehydes and β-keto-acids in buffered aqueous solution at 25° and discussed the possible rôle of this type of condensation in biosynthesis.

In our work, the first example was the preparation of benzylideneacetophenone from benzaldehyde and acetophenone, both of which occur naturally. No precipitation took place at acid pH, but at pH 13 a 96% yield of the pure product resulted; at pH 12, the yield was 52% of a slightly impure product, and at pH 11 no product was obtained. Thus it appeared that, if this type of condensation is to take place at a pH less than 12, compounds containing a more active methylene group must be sought. This led to a consideration of reactions of the Knoevenagel type.

As far back as 1909, Dakin (*J. Biol. Chem.*, **7**, 49) had carried out a number of Knoevenagel reactions in aqueous alcohol at 37° or 100°, using amino-acids as catalysts, the object being the same as ours—to find out if reactions of this type, catalysed by well-known cell constituents, could have any place in cell metabolism. The catalytic effect of amino-acids on condensations of this general type has been noted in more recent work (Fischer and Marschall, *Ber.*, 1931, **64**, 2825; Blanchard, Klein, and MacDonald, *J. Amer. Chem. Soc.*, 1931, **53**, 2809; Kuzin and Nevraeva, *Biochimia*, 1939, **4**, 142; 1941, **6**, 261). These workers, like Dakin, stressed the possible biochemical importance of this activating influence of glycine and other amino-acids.

It was therefore decided to study the influence both of pH and of glycine on condensations of the Knoevenagel type. Furfuraldehyde, which occurs naturally, was chosen on account of its very active aldehyde group and its convenient solubility in water, and was condensed with two compounds containing methylene groups activated on both sides, namely, malonic acid, which is found in some plants, and acetylacetone. Aqueous solutions of furfuraldehyde and malonic acid reacted only in the presence of glycine; furfurylidenemalonic acid (VII) was then

(VII)  (VIII) 

precipitated in 61% yield. It was, however, unsuitable for an accurate pH and catalytic study, owing to its indefinite melting point.

The second product, furfurylideneacetylacetone (VIII), proved suitable for more accurate examination (its constitution is assumed by analogy with other acetylacetone condensation

products). When saturated aqueous solutions of furfuraldehyde and acetylacetone are mixed alone, the natural pH of the solution is 4·1. Overnight an emulsion starts to form, and this slowly crystallises over a period of days. The oil may be the intermediate aldol. The variation of the yield with the duration of the experiment at the natural pH 4·1 is shown in Table VIII.

TABLE VIII.

Furfurylideneacetylacetone (VIII) *from furfuraldehyde* (0·96 *g.*) *and acetylacetone* (1·0 *g.*) *in water* (20 *c.c.*) *at the natural* pH (4·1), *at room temp. M. p.* 55—57° (*pure*).

Duration, days	3	6	10	14
Yield, g.	0·31	0·78	1·06	1·20
Yield, %	17	44	60	67
M. p.	55—57°	←	54—57°	→

The effect of pH is shown in Table IX. The product was obtained in 60—76% yield in the pH range 3·6—6·5, but was not pure. Two points emerge from these results. (i) Formation of the product, without added reagent or ions, supports the view stated above that such a con-

TABLE IX.

Furfurylideneacetylacetone (VIII) *from furfuraldehyde* (0·96 *g.*), *and acetylacetone* (1·0 *g.*) *in buffer solution* (20 *c.c.*); 6 *days at room temp. M. p.* 55—57° (*pure*).

Buffer	N-NaOAc–N-HCl		N-NaOAc–N-AcOH			N-KH_2PO_4–N-NaOH		
Initial pH	2·0	3·6	3·7	4·1	4·7	6·5	7·7	8·5
Final pH	1·0	3·4	3·7	4·1	4·7	6·5	7·4	8·2
Yield, g.	oil	1·11	1·06	1·18	1·35	1·23	oil	oil
Yield, %	—	62	60	66	76	69	—	—
M. p.	←	54—57° →		← 52—55° →		50—53°		

densation might occur if the aldehyde and methylene groups are sufficiently reactive. (ii) This particular Claisen–Knoevenagel condensation to give (VIII) takes place only under acid conditions (pH 3·6—6·5), supporting the acid-catalysed mechanism.

The effect of glycine as a catalyst on the reaction is recorded in Table X, no buffer being

TABLE X.

Furfurylideneacetylacetone (VIII) *from furfuraldehyde* (0·96 *g.*), *acetylacetone* (1·0 *g.*) *and glycine, in water* (20 *c.c.*); 3 *days at room temp. M. p.* 55—57° (*pure*).

Glycine, g.	0	0·1	0·15	0·25	0·5	1·0	1·5	2·0 *
pH	4·1	4·3	4·3	4·4	4·5	4·5	4·6	4·7
Yield, g.	0·31	1·0	1·05	1·07	1·20	1·47	1·50	1·63
Yield, %	17	56	59	60	67	83	84	92
M. p.	←			55—57°				→

* 25 C.c. of water used.

used. The emulsion first precipitated started to crystallise within a few hours, compared with days when glycine was omitted, and the product was always pure. The slight gradual changes observed in the pH from the natural value of 4·1 must be due to the presence of the comparatively large amounts of glycine. From Table IX it can be deduced that the slight increase in pH in Table X from 4·1 to 4·7 cannot be responsible for the large observed increase in the yield; that it must thus be due to the glycine, the catalytic effect of which is best seen by comparing the first two columns in Table X. In the later columns, with the larger amounts of glycine, a salting-out effect may also be operating. No satisfactory explanation of the glycine catalysis can be offered. The glycine may act by combining with the aldehyde to form a loose, reversible addition product (cf. Gulland and Mead, *J.*, 1935, 210), the regenerated aldehyde molecules being suitably activated (cf. Kuzin and Nevraeva, *locc. cit.*).

(d) *Combination of* C–N *and* C–C *Condensations to give Pyrrole and Pyridine Derivatives.*

Pyrroles.—Robinson (*locc. cit.*) has produced some convincing evidence for the origin of the pyrrole nucleus in a large number of alkaloids from the skeleton of the amino-acid ornithine.

The origin of the pyrrole nuclei present in pyrrole pigments has recently been the subject of many reviews, the latest by Granick (*Ann. Rev. Plant Physiol.*, 1951, **2**, 115). Conclusive evidence from biological tracer experiments has been produced that the nitrogen and the methylene-carbon atoms of glycine, but not the carboxyl-carbon atom, are involved in the

biosynthesis and appear in the pyrrole rings intact in the 1 : 2-positions, and below the propionic acid or vinyl side-chains. From present knowledge of the general metabolic activity of glycine (Bentley, *Ann. Reports*, 1948, **45**, 241; Swanson and Clark, *loc. cit.*), no clue can be obtained regarding the entity employed in the biosynthesis of the pyrrole nuclei—whether glycine itself reacts, directly or through some active derivative. Concerning the nature of the other unit or units immediately involved with glycine in the biosynthesis, there is at present no direct experimental evidence; but in theoretical approaches designed to form the postulated common pyrrole precursor, α-ketoglutaric acid and the semialdehyde of succinic acid have been suggested, the interactions being assumed to be brought about in part by oxidative condensations.

This biological work with glycine has brought into prominence three chemical investigations in which glycine under mild conditions is said to give pyrrole-type derivatives, but in no case was a conclusive result obtained (Errera and Greenstein, *Arch. Biochem.*, 1947, **14**, 477; 1947, **15**, 445; *J. Nat. Cancer Inst.*, 1947, **8**, 39; Fu, Price, and Greenstein, *Arch. Biochem. Biophys.*, 1951, **31**, 83; Kuzin and Guseva, *Biochimia*, 1948, **13**, 27; Fischer and Fink, *Z. physiol. Chem.*, 1944, **280**, 123). It is relevant that a successful pyrrole synthesis under comparatively mild conditions, but using the more reactive α-aminoacetoacetic ester in place of glycine, was carried out by Kondo, Ono, and Sato (*J. Pharm. Soc. Japan*, 1937, **57**, 1).

In the present search for milder conditions three sets of starting units (A, B, and C) were

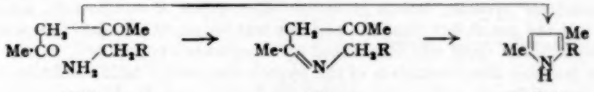
Method A.

Method B.

Method C.

examined : the [Method B, as already mentioned, properly belongs to section (a) but is placed in the present section for convenience].

Method A. The work of Fischer and Fink (*Z. physiol Chem.*, 1944, **280**, 123) with glycine and formylacetone was repeated, and similar inconclusive results obtained. Glycine analogues containing a more active methylene group were therefore selected, *viz.* : aminoacetonitrile and glycine ester hydrochloride. In both of these, unlike glycine, the amino-group is not involved in zwitterion formation with the β-carbon group, and the latter is therefore available to activate the α-methylene group. Acetylacetone was chosen instead of formylacetone, since as it is a symmetrical compound only one product can result, and because the expected derivatives, which if formed would be precipitated from solution, could be synthesised more easily by conventional methods for comparison. The condensation of the two reactants to give a pyrrole involves a combination of a Schiff base and a Claisen–Knoevenagel condensation. The pyrrole might be formed by simultaneous condensation or through the intermediate Schiff base, thus :


(IX) (X) (XI)

The reaction between aminoacetonitrile and acetylacetone was first studied over an approximate pH range (see Table XI). The product was precipitated within the pH range ~5·6—8·7, the maximum yield (69%) of slightly impure product being obtained at pH ~8·0—8·7. It was, however, the Schiff base (X; R = CN). At pH above 9·3, a feeble Ehrlich test

TABLE XI.

4-Cyanomethyliminopentan-2-one (X; R = CN) *from aminoacetonitrile hydrogen sulphate* (1·54 *g.*) *and acetylacetone* (1·0 *g.*) *in aq.* K_2CO_3 (20 *c.c.*); 8 *days at room temp. M. p.* 112—113° (*pure*).

K_2CO_3, g.	0·2	0·3	0·5	0·7	1·0	1·4	2·0	3·0	5·0	6·0
Initial pH	4·4	5·6	5·8	6·9	7·2	8·0	8·7	9·3	10	>10
Final pH	4·4	4·5	4·6	5·8	8·0	8·7	8·6	9·2	10	>10
Yield, g.	0	0·19	0·52	0·92	0·94	0·96	0·86	*	*	*
Yield, %	0	14	38	67	68	69	62	—	—	—
M. p.		← 108—111° →			← 110—112° →					

* Trace of high-melting compound.

was obtained on warming. When kept, these solutions deposited a trace of a high-melting compound which did not give the Ehrlich test. The Schiff base being slightly impure, no further examination of the reaction was made.

Glycine ethyl ester hydrochloride was condensed with acetylacetone in buffer solutionnot be account of the appreciable solubility of the product in water, excess of the buffer could . On

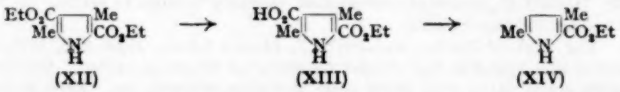
TABLE XII.

4-Carbethoxymethyliminopentan-2-one (X; R = CO_2Et) *from glycine ethyl ester hydrochloride* (1·40 *g.*), *and acetylacetone* (1·0 *g.*) *in buffer solution* (N-KH_2PO_4–N-NaOH) (20 *c.c.*); 2 *days at room temp. M. p.* 66—68° (*pure*).

Initial pH	7·1	7·5	7·7	8·3	8·7	9·0
Final pH	4·5	5·8	6·0	6·5	7·4	8·3 *
Yield, g.	0	0·17	0·39	0·88	0·85	0
Yield, %	0	9	21	48	46	0
M. p.		←	66—68°		→	

* Feeble Ehrlich reaction obtained.

used in this case and accurate buffering was not achieved. Results are given in Table XII. As in the first example, the compound was found to be a Schiff base (X; R = CO_2Et) and not the pyrrole. It was formed only within the limited pH range ~6—8·7 and in every case was obtained pure. The maximum yield at pH 8·3 (falling to 6·5) was 48%; when allowance is made for the considerable solubility of the product in water, this represents the maximum possible. Neither the product itself, nor any of the filtrates from which it was obtained, responded to the Ehrlich test. At pH 9·0, however, no Schiff base was precipitated

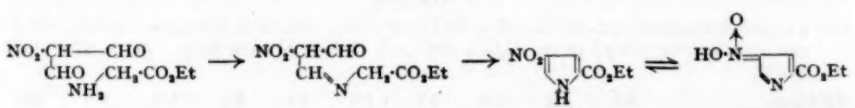


(XII) (XIII) (XIV)

and the solution gave a feeble Ehrlich reaction. In order to study the properties of the expected pyrrole (XIV), it was prepared by use of the normal drastic reagents: (*a*) by ring closure (X ⟶ XI; R = CO_2Et) with boiling alcoholic sodium ethoxide in 20% yield; and (*b*) by the known route from Knorr's widely used starting material in the pyrrole series (XII), by partial hydrolysis with concentrated sulphuric acid to (XIII), followed by distillation to give (XIV). This crystalline pyrrole was found to have a solubility in water of 0·04 g. per 100 c.c. Comparison of the Ehrlich colour given by a saturated solution of (XIV) and the reactant solution (pH 9·0) above showed that, if the Ehrlich colour in the latter is due to the expected pyrrole, it cannot be formed in greater amount than 0·5%. The Ehrlich test is not absolutely specific for pyrroles, but is given by other types of compounds, among which are some phenols, but the possibility that the positive test obtained was due to a self-condensation product of acetylacetone itself was eliminated by a separate experiment.

Since it was possible that formation of the pyrrole ring under mild conditions would require treatment at two different pH's, the crystalline Schiff base itself was shaken with buffer solutions at pH between 9 and 13. The substance dissolved rapidly but no Ehrlich test was obtained, even on long storage.

Attention was next directed to the activation of the ketonic rather than of the glycine component, sodionitromalondialdehyde being selected. Its condensation with glycine ethyl ester hydrochloride, to give the pyrrole (XVI), either directly or through the intermediate Schiff base (XV), was effected by Hale and Hoyt (*J. Amer. Chem. Soc.*, 1915, **37**, 2546; see also Hale and Honan, *ibid.*, 1919, **41**, 770; Hale and Britton, *ibid.*, p. 1020), but under relatively

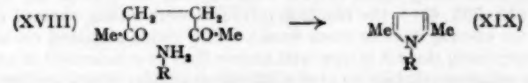


(XV) (XVI) (XVII)

drastic conditions. This work was repeated by us under mild aqueous conditions. The Schiff base was obtained in 65% yield (crude) by mixing the aqueous solutions of the reactants in the cold and leaving them overnight. The pyrrole was obtained in 32% yield (crude) by

immediately bringing the slightly acid solution of the reactants to pH 9·6. As sodionitromalondialdehyde is very difficult to obtain pure and the free aldehyde is unstable, this reaction was unsuitable for accurate study. In addition, nitropyrroles such as (XVI), although they contain a free α-position, do not respond to the Ehrlich test, probably because (Fischer and Orth, " Die Chemie des Pyrrols," Akad. Verlagsges., Leipzig, 1934, Vol. I, p. 108) they can exist in the *aci*-form (XVII); the absence of this useful test removes a valuable and quick method of determining whether or not ring-closure to a pyrrole has taken place. Enough encouragement has been obtained, however, from these successful rough experiments to indicate that the methylene group in glycine ethyl ester is sufficiently active to condense with the carbonyl group of an aldehyde group under mild aqueous conditions. Search is now being made for a suitably active, stable, symmetrical 1 : 3-diketo-compound for more accurate study.

Method B. The widely used Knorr–Paal method for preparing pyrroles, by condensing primary amines with 1 : 4-diketones (XVIII ⟶ XIX) usually requires vigorous conditions.



The crude products, although sometimes obtained in good yield, often require repeated recrystallisation. One case has however been recorded where the conditions employed were milder: diethyl 3 : 6-diketo-octanedioate, when warmed with aqueous methylamine, gives 1-methylpyrrole-2 : 5-diacetic ester in good yield (Willstätter and Pfannenstiel, *Annalen*, 1921, **422**, 14).

It has now been found that the Knorr–Paal reaction proceeds smoothly in aqueous solution at room temperature with reactants chosen to give crystalline products. The 1 : 4-diketone selected was acetonylacetone; this has never been isolated from a natural source and it has been found difficult to trace naturally occurring open-chain compounds containing the grouping $CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO$ in the form of a diketone, dialdehyde, or keto-aldehyde. Although octane-3 : 6-dione has been isolated from wood spirit (Pringsheim and Leibowitz, *Ber.*, 1923, **56**, 2036) it is probably only a product of the destructive distillation. Succindialdehyde, used by

TABLE XIII.

1-*Benzyl*-2 : 5-*dimethylpyrrole* (XIX; R = CH_2Ph) *from benzylamine* (1·07 *g.*) *and acetonylacetone* (1·14 *g.*) *in water* (*approx.* pH *attained by* AcOH *or* NaOH), *then made up to* 200 *c.c. with buffer solution*; 7 *days at room temp.* *M. p.* 46—48° (*pure*).

Buffer	N-NaOAc–N-AcOH		0·2N-KH_2PO_4–0·2N-NaOH					
pH, initial and final	4·4	5·1	5·8	7·1	8·2	9·2	10·9	11·5
Yield, g.	0	0	0	0·02	0·09	0·28	1·30	1·25
Yield, %	0	0	0	1	5	15	70	68
M. p.			⟵			46—48°		⟶

TABLE XIV.

2 : 5-*Dimethyl*-1-*phenylpyrrole* (XIX; R = Ph) *from aniline* (0·93 *g.*) *and acetonylacetone* (1·14 *g.*) *in water* (*approx.* pH *attained by* AcOH *or* NaOH), *then made up to* 100 *c.c. with buffer solution*; 8 *days at room temp.* *M. p.* 51—52° (*pure*).

Buffer	N-NaOAc–N-HCl		N-NaOAc–N-AcOH		0·2N-KH_2PO_4–0·2N-NaOH					
pH, initial and final	3·5	4·0	4·4	5·5	6·4	7·2	8·2	9·3	11·0	11·6
Yield, g.	0·88	1·07	1·19	1·19	0·46	0·19	0	0	0	0
Yield, %	51	63	70	70	27	11	0	0	0	0
M. p.	⟵		51—52°		⟶					

Robinson in his mild chemical synthesis of tropinone, has been postulated (*locc. cit.*) by him to be derived in the cell from ornithine or 1 : 4-diaminoadipic acid. Neither the latter acid nor αα′-diketoadipic acid has been detected in biological material, although the diketo-acid has received consideration as an intermediate in pyruvic ⟶ succinic acid metabolism (Bennet-Clark, *Ann. Rev. Biochem.*, 1937, **6**, 583; Wille, *Annalen*, 1939, **538**, 237).

When a 10% solution of acetonylacetone (pH 5·5) was mixed with either 10% benzylamine (pH 11·3) or saturated aniline solution (with acetic acid added to pH *ca.* 4), the reaction commenced almost immediately and the pyrroles (XIX; R = CH_2Ph and Ph) were deposited

as an emulsion, which rapidly crystallised. The pure products were obtained directly and the yields were respectively 62% and 55% after 1 day, and 92% and 91% after 14 days. The results of an accurate study using buffer solutions are given in Tables XIII and XIV. With the aliphatic amino-group of benzylamine the formation of the pyrrole occurs only in alkaline solution (maximum yield, 70% of pure product at pH 10·9). This is in striking contrast to the results obtained with the aromatic amino-group of aniline, where pyrrole formation takes place best in acid solution (maximum yield, 70% of pure product at pH 4·4—5·5). No satisfactory explanation can be offered for this observation.

Method C. Knorr's extensively used second method for synthesising pyrroles consists in the condensation of an α-amino-ketone, prepared *in situ* by reduction of a hydroxyimino-ketone with zinc and acetic acid, with a β-diketone or a β-keto-ester. Better yields are obtained if the amino-ketone itself, in the form of a salt, is used. Normally the reactants are heated with sodium acetate in 75% acetic acid. It was shown later that strong aqueous alkali could also be employed as the condensing agent (Piloty and Blömer, *Ber.*, 1912, **45**, 3749; Piloty and Hirsch, *Annalen*, 1913, **395**, 63): the reaction mixtures were either warmed gently or kept at room temperature for several days or even weeks. The yields obtained on use of alkali were poor, which is not surprising since it is now well known that two molecules of an α-amino-ketone cyclise in neutral or alkaline solution to give a dihydropyrazine, which oxidises when kept to a pyrazine derivative. Fischer and Orth (*op. cit.*, Vol. I, p. 178) have drawn attention to the fact that, in certain cases where two units can condense in two different ways, Knorr's method gives different pyrroles according to whether acid or alkaline conditions are used; and they describe a condensation in which the pH was kept at 6. A recent application of this modification of Knorr's method has been reported by Corwin and Krieble (*J. Amer. Chem. Soc.*, 1941, **63**, 1831).

Since both acid and alkali appear to catalyse this type of condensation, it was considered that a study of such a reaction in aqueous solution over a pH range might be of interest. The reaction between ω-aminoacetophenone (as hydrobromide) and ethyl acetoacetate, to give the known compound ethyl 2-methyl-4-phenylpyrrole-3-carboxylate (XX), was selected. No naturally occurring α-amino-ketones can be traced, but the system might well be formed in the cell as an intermediate by a route similar to Knorr's, *e.g.*, $CO{\cdot}CH_2 \xrightarrow{\text{nitrite}} CO{\cdot}C{:}N{\cdot}OH \xrightarrow{\text{reduction}} CO{\cdot}CH{\cdot}NH_2$. Ethyl acetoacetate is not known in Nature, but the free acid is a well-known metabolite. As in method A, this condensation could be regarded as a combination of a Schiff base and a Claisen–

(XX)

Knoevenagel reaction. Since the methylene group involved in the present case is activated on both sides, the Claisen–Knoevenagel part of the reaction might be expected to proceed more easily, and in fact the double condensation to give the expected pyrrole readily took place. The results of an accurate pH study with buffer solutions are shown in Table XV. It is of interest that the pyrrole is formed over the wide pH range 3·9—8·2, the highest yield of the slightly

TABLE XV.

Ethyl 2-methyl-4-phenylpyrrole-3-carboxylate (XX) *from ω-aminoacetophenone hydrobromide* (0·60 *g.*) *and ethyl acetoacetate* (0·36 *g.*) *in buffer solution* (50 *c.c.*); 3 *days at room temp. M. p.* 104—106° (*pure*).

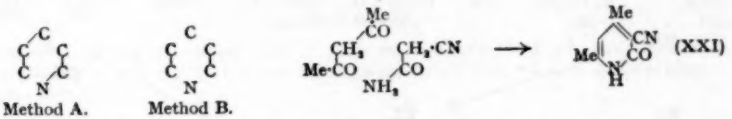
Buffer	N-NaOAc–N-AcOH				N-KH_2PO_4–N-NaOH					
pH, initial and final ...	3·9	4·5	5·5	6·1	6·3	6·6	6·9	7·2	7·8	8·2
Yield, g.	0·01	0·02	0·08	0·09	0·18	0·24	0·40	0·40	0·40	0·40
Yield, %	2	3	13	14	28	38	63	63	63	63
M. p.	←		103—105°		→			←	102—105°	→

impure product (63%) being obtained at pH 6·9. On the alkaline side (pH 7·2—8·2), the product is probably contaminated by some dihydropyrazine.

Pyridines.—Approaches to the biosynthesis of pyridine derivatives have been confined to some pyridine alkaloids, and the widely distributed vitamins nicotinamide and pyridoxine. Robinson (*locc. cit.*) has produced arguments for the biological origin of the pyridine nucleus of some alkoloids from lysine, and successful alkaloid syntheses under mild conditions, carried out

by Robinson, and by Schöpf (*locc. cit.*) and Anet, Hughes, and Ritchie (*locc. cit.*), strongly support the theory. The present evidence for the origin of nicotinamide favours 3-hydroxyanthranilic acid as the probable immediate precursor (Stokstad and Jukes, *Ann. Rev. Biochem.*, **1949**, **18**, 444; Mitchell, " Vitamins and Hormones," 1950, Vol. VIII, p. 140). For pyridoxine the only evidence so far presented is that neither alanine (Holden and Snell, *J. Biol. Chem.*, **1949**, **178**, 799) nor α-formiminopropionic acid (Shive and Shive, *J. Amer. Chem. Soc.*, **1946**, **68**, 117) is a precursor.

In the present work it has been shown that the pyridine ring system can be synthesised under mild aqueous conditions at room temperature from two units (method A), or from four units (method B).



Method A. Method B.

Method A. One of the most fruitful methods for synthesising pyridine compounds is that involving the condensation of cyanoacetamide with a 1 : 3-diketone, -keto-ester, or -keto-aldehyde. Normally the reactants are heated in alcohol with piperidine, but refluxing in water with piperidine acetate has been used (Mariella and Kvinge, *J. Amer. Chem. Soc.*, 1948, **70**, 3126). Milder conditions were used by Sen-Gupta (*J.*, 1915, **107**, 1347). Condensation of acetylacetone and cyanoacetamide to 3-cyano-4 : 6-dimethyl-2-pyridone (XXI) (Wagtendonk and Wibaut, *Rec. Trav. chim.*, 1942, **61**, 728) was selected for a pH study. Difficulties were experienced here with buffering action on the alkaline side, and a large volume of the buffer, with consequent reduction in yield, had to be used at alkaline pH. At nearly neutral or slightly acid pH, it was necessary to employ smaller volumes of buffer in order to obtain the product. Although accurate buffering was achieved in every case, no exact picture of the influence of pH on the yield could be obtained by this method, owing to the varying dilution. A second series of experiments was therefore carried out with rough adjustment of the pH by means of different quantities of potassium carbonate, the volume being kept constant. The results of the two series are given in Tables XVI and XVII. The highest yield obtained by the more accurate

TABLE XVI.

3-Cyano-4 : 6-dimethyl-2-pyridone (XXI) *from cyanoacetamide* (1·68 *g.*) *and acetylacetone* (2·0 *g.*) *in buffer solution* (700 *c.c.*) (N-KH_2PO_4–N-NaOH); 1 *day at room temp.* *M. p.* 288—289° (*pure*).

pH, initial and final	6·4 [a]	7·4 [b]	8·4	9·1	10·5
Yield, g.	0·60	0·85	1·18	2·19	1·23
Yield, %	20	29	40	74	42
M. p.	← 288—289° →				

[a] 40 c.c. of buffer used; no precipitate in 700 c.c. [b] 300 c.c. of buffer used; trace of precipitate in 700 c.c.

TABLE XVII.

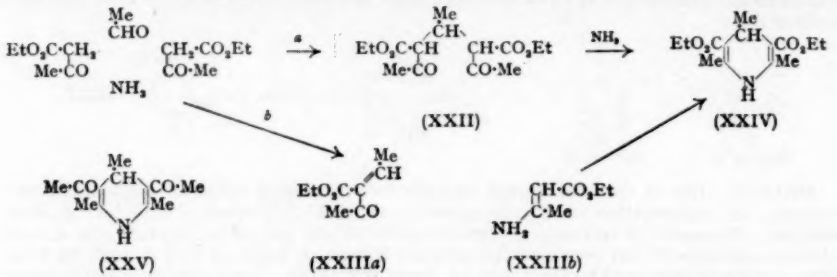
3-Cyano-4 : 6-dimethyl-2-pyridone (XXI) *from cyanoacetamide* (1·68 *g.*) *and acetylacetone* (2·0 *g.*), *and* K_2CO_3 *in water* (40 *c.c.*); 1 *day at room temp.* *M. p.* 288—289° (*pure*).

K_2CO_3, g.	0	0·04	0·06	0·1	0·4	0·8	1·2	1·5	2
Initial pH	4·4	6·4	7·1	7·7	8·5	8·6	8·9	9·0	9·1
Final pH	4·4	6·6	7·2	8·5	10	9·8	10	10	10
Yield, g.	0	0·80	1·35	2·48	2·83	2·89	2·84	2·83	2·79
Yield, %	0	27	46	84	96	98	96	96	94
	← 288—289° →								

buffering method (Table XVI) was 74% at pH 9·1. By the rough method (Table XVII), reasonable control of pH was attained; the highest yield, rising to 98%, was obtained at pH *ca.* 8·5—10. In both cases the product is formed in 20—27% yield on the acid side, at pH about 6·4. In all experiments it was obtained pure directly.

Method B. *The Hantzsch dihydropyridine synthesis.* The reactions so far described have in every case been concerned with the condensation between two molecules only. For study of reactions involving more than two molecules, the Hantzsch dihydropyridine synthesis was

selected (Hantzsch, *Annalen*, 1882, **215**, 8); its exact mechanism is still in doubt. For the condensation between two molecules of ethyl acetoacetate and one of aldehyde-ammonia, to give diethyl 1 : 4-dihydrocollidine-3 : 5-dicarboxylate (XXIV), there is supporting evidence for either mechanism *a* or *b*. The first stage of route *a*, the formation of the 1 : 5-diketone (XXII), is a well-known type of condensation which may proceed in one stage or by a preliminary Claisen–Knoevenagel condensation between one molecule each of acetaldehyde and ethyl acetoacetate to give ethyl α-ethylideneacetoacetate (XXIII*a*), followed by a Michael condensation of this product with a second molecule of the β-keto-ester: the second stage—



(XXII) (XXIV) (XXV) (XXIII*a*) (XXIII*b*)

the action of ammonia on the 1 : 5-diketone to give the dihydropyridine (XXIV)—although well-supported by examples, led to much controversy in the older literature in cases like the present, owing to the possibility of internal condensation in the diketone in presence of basic reagents to give *cyclo*hexane instead of (or as well as) pyridine derivatives. In the case under discussion Rabe and Elze (*Annalen*, 1904, **332**, 19) stated that treatment of the diketone (XXII) with alcoholic ammonia resulted in both types being formed, although they only described the isolation of the dihydropyridine. In favour of mechanism *b*, it is known that, at low temperature in presence of piperidine, acetaldehyde and ethyl acetoacetate can form (XXIII*a*) (Knoevenagel, *Ber.*, 1898, **31**, 735; Auwers and Eisenlohr, *J. pr. Chem.*, 1911, **84**, 100), and also that ammonia and ethyl acetoacetate under certain conditions can give ethyl β-aminocrotonate (XXIII*b*). Although neither of these intermediates has been isolated from the Hantzsch synthesis reaction mixture, it was shown by Beyer (*Ber.*, 1891, **24**, 1662; cf. Knoevenagel, *loc. cit.*, p. 738) that, when prepared separately and then mixed, they readily gave the dihydropyridine (XXIV).

In the preparation of (XXIV) Hantzsch heated the aldehyde-ammonia and the keto-ester without a solvent to the boiling point. Phillips (*J. Amer. Chem. Soc.*, 1949, **71**, 4003) has recently carried out some syntheses by mixing one molecule of various aromatic aldehydes with two of ethyl acetacetate in an equal volume of ethanol, adding two volumes of concentrated aqueous ammonia, and then heating; he states that the yields obtained in this way are better than those obtained by treating the aldehyde with two molecules of ethyl β-aminocrotonate or with one of ethyl β-aminocrotonate and one of ethyl acetoacetate.

As two typical examples of the Hantzsch synthesis, the preparation of diethyl 1 : 4-dihydrocollidine-3 : 5-dicarboxylate (XXIV) and of 3 : 5-diacetyl-1 : 4-dihydrocollidine (XXV) was selected for pH study in aqueous solution. The results for compound (XXIV) prepared from acetaldehyde, ethyl acetoacetate, and ammonia are shown in Table XVIII. A large volume of buffer solution was required for satisfactory buffering. With the reactants in theoretical amounts the pure compound (XXIV) was formed within the pH range 6—10, the highest yield (43%) being obtained at pH 8·5. Since this pH is close to that of 10% aqueous ammonium carbonate

TABLE XVIII.

Diethyl 1 : 4-*dihydrocollidine*-3 : 5-*dicarboxylate* (XXIV) *from acetaldehyde* (0·44 *g.*), *ethyl acetoacetate* (2·60 *g.*) *and ammonia* (d 0·88; 0·17 *g.*) *in buffer solution* (N-KH_2PO_4–N-NaOH) (500 *c.c.*); 4 *days at room temp.* *M. p.* 129—130° (*pure*).

pH, initial and final	5·5	6·0	7·1	7·5	8·5	10[a]
Yield, g.	0	0·08	0·47	0·89	1·15	0·55
Yield, %	0	3	18	33	43	21
M. p.		←	129—130°		→	125—127°

[a] Fell to 8·9.

(9·2), the condensation was also performed in a different way, with a view to its possible use as a preparative method. The reactants were dissolved in the minimum amount of 10% ammonium carbonate solution, thus ensuring a large excess of ammonia (pH during the experiment 8·5). The slightly yellow product was washed with acid to remove a yellow basic impurity, and yielded 70% of nearly pure pyridine derivative.

The results for the second example, the condensation, in buffer solutions, of the theoretical amounts of acetaldehyde, acetylacetone, and ammonia to give (XXV), are shown in Table XIX. The pure product was formed within the pH range 5·5—9·3, with a maximum yield of 29% over the range 6·6—8·5. In this case, a reasonable volume of buffer sufficed to maintain the pH within fairly accurate limits.

TABLE XIX.

3 : 5-*Diacetyl*-1 : 4-*dihydrocollidine* (XXV) *from acetaldehyde* (0·44 *g.*), *acetylacetone* (2·0 *g.*), *and ammonia* (d 0·88; 0·17 *g.*) *in buffer solution* (100 *c.c.*); 4 *days at room temp. M. p.* 152—153° (*pure*).

Buffer	N-NaOAc–N-AcOH	N-KH_2PO_4–N-NaOH								
Initial pH	5·5	6·0	6·3	6·6	7·1	8·0	8·5	9·0	9·3	10
Final pH	5·5	6·0	6·3	6·3	7·0	7·5	8·1	8·6	8·6	9·0
Yield, g.	0·02	0·24	0·50	0·59	0·59	0·59	0·60	0·47	0·23	0
Yield, %	1	12	24	29	29	29	29	23	11	0
M. p.	←	←	←	←	152—153°	→	→	→	→	→

The experiment was repeated with 10% aqueous ammonium carbonate solution replacing the theoretical amount of ammonia, with the object of seeking a useful preparative method as before. The condensation proceeded at pH 8·1 more slowly than in the corresponding preparation of (XXIV), but a 51% yield of pure (XXV) was obtained. In contrast to the first example performed under these conditions, no by-product contaminated the product.

In view of the number of different ways in which the four molecules taking part in these Hantzsch syntheses could react with themselves or with one another, it is perhaps surprising that the reaction proceeds so smoothly in aqueous solution and gives such good yields.

Since the suggested mechanism for both types of condensation (methods A and B) involves reactions which are usually considered to be of the base-catalysed type, it is of interest that the products are formed at acid as well as alkaline pH.

EXPERIMENTAL.

General.—Experiments recorded in Tables I—XX were performed in stoppered flasks at room temperature (average 18°). The starting materials were purified by distillation or crystallisation just before use. After the times stated, which were found after a number of trials, the products were separated by filtration, washed with a small amount of water, and dried for 1—2 days at room temperature in a vacuum-desiccator. The filtrates were set aside for a further period, in order to ensure that no appreciable additional amounts of the products were deposited. Yields and m. p.s, unless stated otherwise, are for these initial untreated products. Each product was also prepared by the usual methods described in the literature, and the two samples were proved to be identical by mixed m. p. All m. p.s are corrected.

Analyses.—All our products were analysed, the specimen used being obtained from a mixture of all the pure samples from the various ranges of pH. Before analysis, each specimen was finely powdered and dried at room temperature in a vacuum-desiccator for 5 days.

Solubilities of Reactants in Water at Room Temperature (Average 18°).—Most of these were already known. Solubilities not listed or uncertain were, in g. per 100 c.c. of water at room temperature, as follows:

p-Anisaldehyde	0·33	α-Naphthylamine	0·14
p-Hydroxybenzaldehyde	0·81	*o*-Phenylenediamine	2·16
Cinnamaldehyde	0·14		

Buffer Solutions.—The buffer solutions used are those given by Britton ("Hydrogen Ions," 3rd Edn., Chapman and Hall, London, 1942); 0·2N-solutions were used at first, but later N-solutions were found to be more suitable. In each case the reactants were dissolved separately in suitable volumes of the buffer solution, and the pH was measured to ensure that no change had occurred. The reactant solutions were then mixed, and the pH was at once determined again, unless precipitation of the product prevented this. When the reaction was complete, the pH of the filtrate was finally determined yet again.

The Muirhead pH meter, with the usual glass electrode supplied, was used throughout for measurements up to pH 10. In the later work, for pH's >10, the new " Alkacid " glass electrode (Doran Instrument Co., Ltd., Stroud) was substituted.

Schiff Bases.—Details are given in the Table XX. The smaller aqueous solution was added to the larger. After a short interval, normally less than 1 minute, an emulsion usually appeared suddenly and, after occasional shaking, crystallisation commenced. After 1 day (for the second case in the Table, 5 days' storage or 15 hours' shaking after seeding; for the fourth case, 2 days) the product

TABLE XX.

Preparation of Schiff bases, quinoxaline, and diazepine derivatives from saturated aqueous solutions of the reactants.

Amine in water, g./c.c.	Ketone or aldehyde in water, g./c.c.	Limits of pH[a]	Yield, %	M. p.	Formula	Found, % C	Found, % H	Found, % N	Calc., % C	Calc., % H	Calc., % N
Ph·NH_2 9·3/273	Ph·CHO 10·6/3000	4·2—7·6	74	51—52°[b]	$C_{13}H_{11}N$	86·1	6·3	8·0	86·2	6·1	7·7
α-$C_{10}H_7$·NH_2 2·86/2000	Ph·CHO 2·12/600	4·2—7·1	84	72—73	$C_{17}H_{13}N$	88·2	5·5	6·3	88·3	5·6	6·1
Ph·NH_2 2·79/82	*p*-HO·C_6H_4·CHO 3·66/450	4·9—7·6	91	192—193	$C_{13}H_{11}ON$	79·0	5·9	7·2	79·2	5·6	7·1
Ph·CH_2·NH_2 3·21/140[c]	,,	4·9—11·3	81	205—206	$C_{14}H_{13}ON$	79·3	6·6	6·6	79·6	6·2	6·6
Ph·NH_2 2·79/82	*p*-MeO·C_6H_4·CHO 4·08/1250	4·7—7·6	70	61—63	,,	79·3	6·0	6·6	,,	,,	,,
Ph·CH_2·NH_2 5·35/233[c]	*p*-MeO·C_6H_4·CHO 6·8/2083	4·7—11·3	87	40—42	$C_{15}H_{15}ON$	79·7	6·9	6·5	80·0	6·7	6·2
Ph·NH_2 2·79/82	Ph·CH:CH·CHO 3·96/2800	4·9—7·6	85	108—109	$C_{15}H_{13}N$	86·8	6·5	7·0	87·0	6·3	6·8
Ph·NH_2 3·72/109	$CH_2(COMe)_2$ 4/32	3·3—7·6	74	51—53[d]	$C_{11}H_{13}ON$	75·6	7·5	8·0	75·4	7·4	8·0
m-NH_2·C_6H_4·OH 4·36/168	,,	3·3—7·4	84	132—134[d]	$C_{11}H_{13}O_2N$	68·9	6·8	7·5	69·1	6·8	7·3
o-$C_6H_4(NH_2)_2$ 3·24/150	Me·CO·COMe 2·58/10·3	3·5—7·4	93[e]	105—107	$C_{10}H_{10}N_2$	76·2	6·3	17·7	76·0	6·3	17·7
o-$C_6H_4(NH_2)_2$ 5·4/250	$CH_2(COMe)_2$ 5/40	3·3—7·4	36[f]	131—133	$C_{11}H_{12}N_2$[g]	76·8	6·9	16·0	76·7	7·0	16·3

[a] pH of the aldehyde (or ketone) solution given first, followed by pH of the base solution. [b] This is the usual figure given in the literature. Pyl (*Ber.*, 1927, **60**, 287) gives 53·5°, but, using his method, we obtained 51—52°. [c] Large excess of water. [d] Monoanil. [e] Mixture warmed by 4°; 2 : 3-dimethylquinoxaline collected after 5 mins. [f] Colourless hydrate of 5 : 7-dimethyl-2 : 3-benzo-1 : 4-diazepine deposited from violet solution; easily dehydrated in a vacuum-desiccator. Solubility, 0·74 g. per 100 c.c. of water at room temperature. [g] Found: *M* (cryoscopic in C_6H_6), 164. Reqd.: *M*, 172.

was collected. The literature on Schiff bases contains many references to the existence of individuals in two forms, possessing different m. p.s and sometimes different colours. In the older work these were thought to be *cis-trans*-isomers but the later investigations (de Gaouck and Le Fèvre, *J.*, 1939, 1392; Jensen and Bang, *Annalen*, 1941, **548**, 106; van Alphen, *Rec. Trav. chim.*, 1942, **61**, 875) support the view that they are simply different cyrstalline modifications.

2-*Amino*-4 : 6-*dimethylpyrimidine* (III; R = NH_2).—When prepared by Combes and Combes's method (*Bull. Soc. chim.*, 1892, **7**, 788) this melted 152—154° (anhyd.). Our sample (Table IV) was analysed (Found: C, 57·9; H, 7·1; N, 34·2. Calc. for $C_6H_9N_3$: C, 58·5; H, 7·3; N, 34·2%). Solubility, 4·0 g. per 100 c.c. of water at room temperature.

4 : 6-*Dimethyl*-2-*phenylpyrimidine* (III; R = Ph).—When prepared by Pinner's (*loc. cit.*) method this melted at 81—83°. Our sample (Table V) was analysed (Found: C, 78·2; H, 6·0; N, 15·7. Calc. for $C_{12}H_{12}N_2$: C, 78·3; H, 6·5; N, 15·2%).

Benziminazole.—The sample prepared by the method described in *Org. Synth., Coll. Vol.* II, p. 65 had m. p. 169—171°. In our experiments (Table VI), traces of a high-melting mauve substance were deposited, and this was filtered off and discarded before isolation of the benziminazole, by adjustment to pH 8·5—9·0 with ammonia and storage for 4 hours before collection. This substance, which was not investigated further, was not formed when the experiments were conducted in an atmosphere of nitrogen, and is probably an oxidation product of *o*-phenylenediamine. Our sample of benziminazole (Table VI), m. p. 169—171°, was analysed (Found: C, 71·6; H, 5·4; N, 23·4. Calc. for $C_7H_6N_2$: C, 71·2; H, 5·1; N, 23·7%).

4 : 6-*Diamino*-5-*formamidopyrimidine* (V).—Details are given in Table VII. Since this compound had an indefinite m. p., no attempt was made to obtain it by another method for comparison. It was isolated at the conclusion of the experiment by adjustment to pH 8·5—9 with ammonia, and filtering after 4 hours. The products from experiments at various pH's were mixed, dried *in vacuo* at 130° overnight, and analysed (Found: C, 39·2; H, 4·4; N, 45·8. Calc. for $C_5H_7ON_5$: C, 39·2; H, 4·6; N, 45·8%).

When 4 : 5 : 6-triaminopyrimidine (3·1 g.) was dissolved in N-hydrochloric acid (50 c.c.), formic acid (90%, 2 c.c.) added, and the whole kept for 2 days, stout colourless needles of the hydrochloride (1·84 g., 40%) were deposited (Found : C, 32·1; H, 4·1; N, 36·5. Calc. for $C_5H_8ON_4Cl$: C, 31·6; H, 4·2; N, 36·9%). The filtrate, treated with ammonia to pH 8·5—9, gave 1·0 g. (21%) of the free formamido-compound. In connection with the experiments carried out to cause cylisation to adenine, described below, it should be noted that the formamido-compound did not respond to Kossel's test (*loc. cit.*) for adenine.

Adenine.—The above formamido-compound (0·3 g.) was heated at 230° for 4 hours. The product was dissolved in dilute hydrochloric acid, then filtered, and aqueous ammonia added to the filtrate to bring the pH to 8·5—9. The precipitate (0·2 g.) was collected, dried in a vacuum at 130° overnight, and analysed (Found : C, 44·3; H, 3·5; N, 52·5. Calc. for $C_5H_5N_5$: C, 44·5; H, 3·7; N, 51·9%). The identity of this product with adenine was confirmed from its m. p. [351—353° (decomp.)], its response to Kossel's test (*loc. cit.*), and its ultra-violet absorption spectrum in N/20-hydrochloric acid ($\lambda_{max.}$ 2615—2635 Å; $\varepsilon_{max.}$ = 13,150) (cf. Baddiley, Lythgoe, and Todd, *J.*, 1943, 387; Clark and Kalckar, *J.*, 1950, 1030). Attempts were made to cyclise the formamido-compound (0·1 g.) by storing, at room temperature for 7 days, sodium hydroxide solutions of it at pH 14 (2 c.c.), pH 13 (5 c.c.), pH 12 (9 c.c.), and pH 11 (10 c.c.), and then searching for adenine by Kossel's test (*loc. cit.*), but with negative results. At pH 14, with the formamido-derivative (0·50 g.) in 3N-sodium hydroxide (5 c.c.), the original triamino-pyrimidine (0·26 g.), proved by m. p. and mixed m. p. 254—258° (decomp.) (inserted at 245°), was deposited.

Benzylideneacetophenone.—(*a*) Saturated aqueous solutions of benzaldehyde (1·06 g. in 300 c.c.) and acetophenone (1·2 g. in 200 c.c.) were mixed, and a rough pH range 1—11 made up by the addition of acid or alkali. Although on storage for several weeks, the solutions of pH 8—11 became cloudy, no crystalline compound was obtained even after addition of a nucleus of benzylideneacetophenone. Owing to the dilution used, the product could not have been the intermediate aldol, a known crystalline compound (Schöpf and Thierfelder, *loc. cit.*, p. 149). In any case the amount obtained was so small that it did not invite further investigation.

(*b*) Benzaldehyde (1·06 g.) in 0·1N-sodium hydroxide (300 c.c.) was mixed with acetophenone (1·2 g.) in the same solvent (200 c.c.). The mixture (pH 13) rapidly became cloudy, and crystallisation occurred on storage. After 7 days, the product was collected and washed with water. The yield was 2·0 g. (96%), and the m. p. 55—57° (pure) (Found : C, 86·3; H, 6·1. Calc. for $C_{15}H_{12}O$: C, 86·5; H, 5·8%). Repetition of the experiment, but with 0·01N-sodium hydroxide (pH 12), gave 1·08 g. (52%) of low m. p. (53—55°) With 0·001N-sodium hydroxide (pH 11), only a faint cloudiness was obtained after 21 days' storage. The authentic specimen (*Org. Synth., Coll. Vol.* I, p. 78) after crystallisation has m. p. 55—57°.

In attempts to catalyse the condensation with glycine alone, mixed aqueous solutions of benzaldehyde and acetophenone were treated with various amounts of glycine, but no product was precipitated after several weeks' storage.

Furfurylidenemalonic Acid (VII).—To malonic acid (2·1 g.) and glycine (1 g.) in water (15 c.c.) was added furfuraldehyde (1·9 g.). On shaking, the aldehyde went into solution (pH 2·7). Crystallisation commenced overnight, and after 2 days the product (1·6 g., 44%) was collected. After 5 days more, a further yield of 0·63 g. (17%) was obtained. The product was also prepared by Liebermann's method (*Ber.*, 1894, **27**, 285). All samples, alone or admixed, had m. p. 190—205° (decomp.), with darkening from 180° onwards. The sample prepared in aqueous solution was analysed (Found : C, 52·7; H, 3·4. Calc. for $C_8H_4O_4$: C, 52·8; H, 3·3%). On repetition of the experiment, but without glycine, at the natural pH (2·1) of the solution, no precipitation took place, even after 7 days in presence of a nucleus.

Furfurylideneacetylacetone (*3-Acetyl-4-furylbut-3-en-2-one*) (VIII).—Details sufficing for the preparation of this *compound* are given in Tables VIII, IX, and X. The material crystallises in small colourless prisms. The m. p. was not raised by recrystallisation from methanol [Found, for non-recrystallised material : C, 67·2; H, 5·5%; *M* (Rast, and cryoscopic in benzene), 187. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·6%; *M*, 178].

4-Cyaromethyliminopentan-2-one (X ; R = CN).—Most of the details regarding this preparation are given in Table XI. Aminoacetonitrile hydrogen sulphate was obtained by the method described in *Org. Synth., Coll. Vol.* I, p. 298. For analysis the *ketone* was recrystallised from ethanol, the m. p. of the colourless plates being thus raised from 110—112° to 112—113° [Found : C, 60·5; H, 7·1; N, 20·4%; *M* (Rast), 145. $C_7H_{10}ON_2$ requires C, 60·9; H, 7·3; N, 20·3%; *M*, 138].

4-Carbethoxymethyliminopentan-2-one (X ; R = CO_2Et).—Details will be found in Table XII [Found : C, 58·1; H, 8·2; N, 7·8%; *M* (Rast), 190. Calc. for $C_9H_{15}O_3N$: C, 58·4; H, 8·1; N, 7·6%; *M*, 185]. The compound was also prepared by Fischer's method (*Ber.*, 1901, **34**, 438). Solubility, 4·8 g. per 100 c.c. of water at room temperature.

Ethyl 3 : 5-Dimethylpyrrole-2-carboxylate (XIV).—The Schiff base (X ; R = CO_2Et) (2·0 g.) was cyclised by heating it under reflux with sodium (0·25 g.) in ethanol (10 c.c.) for 3 hours (cf. Fischer and Fink, *Z. physiol. Chem.*, 1948, **283**, 152). The solution was poured into water (100 c.c.), and the product filtered off, washed with water, and dried. The yield was 0·35 g. (20%), and the m. p. 124—126° without recrystallisation (Found : C, 64·4; H, 7·4; N, 8·7. Calc. for $C_9H_{13}O_2N$: C, 64·7; H, 7·8; N, 8·4%). The sample prepared by the known method (Fischer and Walach, *Ber.*, 1925, **58**, 2820; see also Corwin and Quattlebaum, *J. Amer. Chem. Soc.*, 1936, **58**, 1083) melted at 122—125° after repeated crystallisation from ethanol. A mixed m. p. confirmed the identity. Solubility, 0·04 g. per 100 c.c. of water at room temperature.

3-Carbethoxymethylimino-2-nitropropaldehyde (XV).—Sodionitromalondialdehyde (Hill and Torrey, *Amer. Chem. J.*, 1899, **22**, 89) (0·31 g.) in water (3 c.c.) was added at room temperature to glycine ethyl

ester hydrochloride (0·28 g.) in water (1 c.c.). Within 5 minutes, the product commenced to crystallise. After 1 hour 0·24 g. (m. p. 97—100°) and after 1 day an additional 0·02 g. (m. p. 98—101°) was obtained (total yield, 65%). Recrystallisation from ethanol (5 c.c.) gave the pure product, m. p. 100—102° alone or mixed with an authentic specimen prepared by the method of Hale and Hoyt, *loc. cit.*, who give m. p. 104° (Found: C, 41·6; H, 4·9; N, 13·9. Calc. for $C_7H_{10}O_4N_2$: C, 41·6; H, 5·0; N, 13·9%).

Ethyl 4-Nitropyrrole-2-carboxylate (XVI).—The same quantities as above were used but, immediately after mixing, the slightly acid solution was brought to pH 9·6 by the addition of 20% aqueous potassium carbonate (5 c.c.). Precipitation of an oil started almost immediately, followed later by crystallisation. Next morning the nitropyrrole (0·12 g., 32%; m. p. 165—170°) was filtered off. Recrystallisation from ethanol (1 c.c.), or water (32 c.c.), gave the pure product, m. p. 170—172° alone or mixed with an authentic specimen prepared by the method of Hale and Hoyt, *loc. cit.*, who give m. p. 174°), not raised by further recrystallisation (Found: C, 46·1; H, 4·3; N, 15·3. Calc. for $C_7H_8O_4N_2$: C, 45·7; H, 4·3; N, 15·2%).

1-Benzyl-2 : 5-dimethylpyrrole (XIX; R = CH_2Ph).—A solution (pH 5·5) of acetonylacetone (5·7 g.) in water (57 c.c.) was added to a solution (pH 11·3) of benzylamine (5·35 g.) in water (214 c.c.). After a few minutes, an emulsion suddenly appeared, which rapidly crystallised. The solution was protected from light. After 1 day, the collected precipitate weighed 5·7 g. (62%) and, in a separate experiment, after 14 days 8·5 g. (92%). The m. p. alone or admixed with an authentic specimen prepared by the method of Hazlewood *et al.* (*J. Roy. Soc. N.S. Wales*, 1937, **71**, 92) who give 48° was 46—48° (Found: C, 83·8; H, 8·5; N, 7·8. Calc. for $C_{13}H_{15}N$: C, 84·3; H, 8·1; N, 7·6%). See also Table XIII.

2 : 5-Dimethyl-1-phenylpyrrole (XIX; R = Ph).—After acetonylacetone (3·42 g.) in water (34 c.c.) and aniline (2·79 g.) in water (82 c.c.) had been mixed, sufficient acetic acid (*ca.* 10 c.c.) was added to bring the pH to *ca.* 4. The solution was protected from light. After 1 day the yield was 2·8 g. (55%), and after 14 days 4·6 g. (91%). The m. p. alone or admixed with an authentic specimen prepared by the method of Hazlewood *et al.* (*loc. cit.*) was 51—52° (Found: C, 84·1; H, 7·5; N, 8·2. Calc. for $C_{12}H_{13}N$: C, 84·2; H, 7·6; N, 8·2%). See also Table XIV.

ω-Aminoacetophenone Hydrobromide.—This was prepared from phenacyl bromide (24 g.) (*Org. Synth., Coll. Vol.* II, p. 480) by Mannich and Hahn's method (*Ber.*, 1911, **44**, 1545: see also Slotta and Heller, *Ber.*, 1930, **63**, 1027, and Lutz *et al.*, *J. Org. Chem.*, 1947, **12**, 106). The crude mixture of ω-aminoacetophenone hydrobromide and ammonium bromide obtained (35·5 g.) was repeatedly crystallised from ethanol, and the product (12·5 g.), m. p. 217° (decomp.), which probably still contained ammonium bromide, was separated.

Ethyl 2-Methyl-4-phenylpyrrole-3-carboxylate (XX).—Prepared by Knorr and Lange's method (*Ber.*, 1902, **35**, 3002) and crystallised from methanol, this had m. p. 104—106°. Our sample, m. p. 103—105° (Table XV), was crystallised once from methanol, and the m. p. after this treatment, alone or admixed with the authentic specimen, was 104—106° (Found: C, 73·8; H, 6·4; N, 6·4. Calc. for $C_{14}H_{15}O_2N$: C, 73·4; H, 6·6; N, 6·1%).

3-Cyano-4 : 6-dimethyl-2-pyridone (XXI).—A specimen prepared by Wagtendonk and Wibaut's method (*loc. cit.*) melted 288—289°. Our sample (Tables XVI and XVII) was analysed (Found: C, 65·2; H, 5·4; N, 19·1. Calc. for $C_9H_8ON_2$: C, 64·9; H, 5·4; N, 18·9%).

Diethyl 1 : 4-Dihydrocollidine-3 : 5-dicarboxylate (XXIV).—The crude product prepared by Hantzsch's method (*loc. cit.*) required repeated crystallisation from ethanol–water (1 : 2) to raise the m. p. to 129—130°. The sample described in Table (XVIII) was analysed (Found: C, 62·6; H, 7·9; N, 5·6. Calc. for $C_{14}H_{21}O_4N$: C, 62·9; H, 7·9; N, 5·2%). For our more approximate method, ethyl acetoacetate (5·2 c.c.) and acetaldehyde (1·2 c.c.) were dissolved in aqueous ammonium carbonate (10%; 100 c.c.; pH 9·2), and left for a day. The initial and the final pH during the experiment were 8·5. The yellow crystalline product was collected and shaken with dilute hydrochloric acid for 5 hours to remove a yellow basic impurity. The resulting colourless material obtained after filtration and washing with water weighed 3·75 g. (70%) and melted at 127—129°.

3 : 5-Diacetyl-1 : 4-dihydrocollidine (XXV).—This was prepared as described by Combes and Combes (*Bull. Soc. chim.*, 1889, **1**, 15; see also Knoevenagel and Ruschhaupt, *Ber.*, 1898, **31**, 1029; Mumm and Petzold, *Annalen*, 1938, **536**, 18); it melted 152—153°. The sample described in Table XIX was analysed (Found: C, 69·0; H, 8·2; N, 6·8. Calc. for $C_{13}H_{17}O_2N$: C, 69·6; H, 8·2; N, 6·8%). For our more approximate method, acetylacetone (2·2 c.c.) and acetaldehyde (0·6 c.c.) were dissolved in aqueous ammonium carbonate solution (10%; 20 c.c.; pH 9·2) and left for 4 days. The initial and the final pH during the experiment were 8·1. The product was collected and washed with water, the yield being 1·0 g. (51%) and the m. p. 152—153° (pure).

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, June 14th*, 1951.]

698. cyclo*Butadiene and Some Other* pseudo*Aromatic Compounds.*

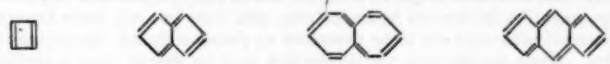
By D. P. Craig.

Conjugated molecules with two fused five-membered rings or two fused seven-membered rings are unknown, in contrast to azulene which has a five- and a seven-membered ring fused together. The first two types are members of a series of molecules at present unknown, for which a general specification can be given, and whose characteristics are discussed. The name *pseudo*aromatic seems appropriate to describe cyclic conjugated molecules of this class, of which the simplest member is *cyclo*butadiene.

It is argued from one case worked out non-empirically in detail and, from more general considerations, that these molecules will not have the π-electron stability expected by analogy with benzene and normal aromatic compounds, and that the enumeration of valence-bond structures and the notion of resonance between them are here of dubious energetic significance. The molecules should not therefore be expected to show typically aromatic properties. They ought, for example, to show marked unsaturation and unequal C–C distances.

*cyclo*Octatetraene is briefly discussed. On these views a molecule with two fused eight-membered rings ought to be a normal aromatic compound, and so to show marked differences from *cyclo*octatetraene, even when proper allowance is made for a strained single-bond framework common to both.

A problem exists in molecular theory as to why none of the structures (I)—(IV) is known. By contrast, azulene, with fused five- and seven-membered rings, is known and displays nearly normal aromatic behaviour. The series (I—IV) can be extended. Its simplest members are those having only peripheral π-electron centres; they have in common that (*a*) the number of

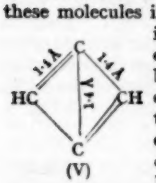


(I) (II) (III) (IV)

carbon atoms providing π-electrons is a multiple of 4, and (*b*) the structures are planar, or nearly so (as far as can be judged from their single-bond frameworks), and have an axis of symmetry passing through two π-electron centres. No molecule which fits this description, and so continues the series of which *cyclo*butadiene is the first member, is yet known. Of known molecules, *cyclo*octatetraene most nearly meets these conditions, and so is an important special case mentioned later in this paper.

Single-bond strain might be supposed decisively important in *cyclo*butadiene,* but it can hardly be so in the other molecules. The problem of existence and stability appears therefore to be bound up with the energetics of the π-electron system. Craig and Maccoll (*J.*, 1949, 964) noted these facts, and studied the π-electron states of pentalene (II) by the empirical valence-bond and molecular orbital methods. These methods disagree even in so fundamental a matter as the identity of the ground state, and so neither can in the first instance be accepted. To get a physically significant account of these systems it is clearly necessary to avoid the prejudices of the empirical methods, which are the special forms of wave function and the use of empirical parameters derived from benzenoid hydrocarbons, and to work instead in a non-empirical way. That is the purpose of this paper. Molecules for which no Kekulé-like structure can be written, such as *m*-quinodimethane, are not considered.

1. *General Energy Considerations.*—At the outset it is natural to approach the study of these molecules in terms of the methods developed for the known aromatic compounds, *i.e.*, in terms of the valence-bond and molecular-orbital methods. In this it is convenient to refer both to the molecules (I)—(IV) and to the corresponding, but hypothetical, monocyclic molecules having $4n$ carbon atoms lying on the circumference of a circle. Finally, it will be necessary to examine the hypothetical *bicyclo*butadiene (V), which may be considered to be the parent of the di- and poly-cyclic molecules (II)—(IV), while *cyclo*butadiene is the parent of the monocyclic ones. These hypothetical molecules have improbable single-bond frameworks, but this is not important here: the π-bonds do not have directional properties in the molecular plane, and examination of the π-electron systems may be illuminating in the study of the principal question.



(V)

* But not, even here, so decisively as might appear: see Coulson and Moffitt, *Phil. Mag.*, 1949, **40**, 1.

The performance of the simple theoretical methods in the molecules (I)—(IV) may be sketched as follows. In the valence-bond theory the lowest π-electron state for these, and for the hypothetical structures referred to above, belongs in each case to a non-totally symmetrical representation of the appropriate symmetry group. All known (plane) aromatic hydrocarbons have, on the contrary, totally symmetrical valence-bond ground states. But these non-totally symmetrical states have resonance energies per π-electron comparable with those of normal aromatic compounds. Further, comparison between one of the molecules (I)—(IV) and the monocyclic molecule with the same number of π-electrons shows that the monocyclic molecule has the larger resonance energy: the additional bond thus reduces the valence-bond resonance energy.

In the molecular orbital theory the distinction between monocyclic and other systems is more important. In the monocyclic systems the ground state is always degenerate. This degeneracy is capable of being split by electronic interaction, which is, however, a correction not envisaged in the simple theory (see Wheland, *Proc. Roy. Soc.*, 1938, *A*, **164**, 397). The resonance energy is smaller than in normal aromatic structures: for example, overlap being neglected, it is zero in *cyclo*butadiene, and 0·2β per π-electron in planar *cyclo*octatetraene, compared with 0·33β in benzene. In the polycyclic systems the degeneracy is split, and the ground state is found to be totally symmetrical, contrary to the valence-bond result. Furthermore, the resonance energy is now greater than in the monocyclic molecule: in *bicyclo*butadiene (V) it is 0·28β, and in pentalene 0·31β, per π-electron. The additional bond increases the molecular-orbital resonance energy.

The situation described for the exceptional molecules (I)—(IV) may be compared with that for the known aromatic compounds in which the predictions of the methods are consistently in agreement in ground-state symmetry and in the differences between monocyclic and polycyclic systems. It appears probable therefore that, on theoretical as well as practical grounds, cyclic structures with alternate single and double bonds may be put into two classes: normal aromatic compounds like the known hydrocarbons, and those in some sense abnormal like (I)—(IV). The abnormal molecules are to be described as *pseudo*aromatic, according to a definition introduced later. Some insight into the distinction may be gained from a preliminary study of the leading members of the two classes, *viz.*, benzene and *cyclo*butadiene, in the following simple way. The source of the potential field for π-electrons is at first supposed to be a uniform circular distribution of positive charge. The wave functions may be approximated as combinations of one-electron orbitals each of which depends on the angle φ, measured in the molecular plane, in the same way as in a diatomic molecule. The dependence on the radial distance, and on the other angle co-ordinate, need not be brought in. In this model, which was first used extensively for aromatic molecules by Platt (*J. Chem. Physics*, 1949, **17**, 484), the effect of interelectronic repulsion may be treated qualitatively. To study, again qualitatively, how the presence of point charges affects the circular field states, it is necessary to add a perturbing potential of the correct symmetry as in Bethe's well-known theory of crystalline potentials (*Ann. Physik*, 1929, **3**, 133). This method of approximation is not good enough for quantitative work but presents the main features of the solutions.

The circular field orbitals are specified by ring quantum numbers m:

$$\phi_m = f(r, \theta)e^{im\varphi} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1.1)$$

The dependence of the radial distance r and the angle θ is supposed the same for all orbitals; this takes the place of the assumption usual in LCAO calculations that the orbitals are made from a single type of atomic orbital, *e.g.*, $2p\pi$. In the lowest configuration of *cyclo*butadiene two electrons occupy ϕ_0 and two $\phi_{\pm 1}$. The states of this configuration are $^1\Sigma$, $^3\Sigma$, and $^1\Delta$. These are split by electron repulsion, giving the scheme shown in the centre column of Fig. 1. Electron repulsion being treated as a perturbation, the splitting is symmetrical and in the sense required by Hund's rule. The levels fall in the same order as in O_2, to which at this stage there is a close analogy. A tetragonal potential, added to the circular field, simulates the effect of the nuclei and removes the remaining degeneracy as shown schematically in the third column of Fig. 1. The simplest such perturbing potential is

$$V = -2a \cos 4\varphi \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1.2)$$

where $2a$ measures the intensity of the perturbation at $\varphi = 0$, and the minus sign means that the sources are positive charges. The perturbation (1.2) splits the $^1\Delta$ wave function of the circular field into two non-degenerate levels Ψ^+ and Ψ^-. Up to terms in the first power of a

the splitting measures the mixing caused by (1.2) between the lowest $^1\Delta$ configuration wave function $\Psi_0(^1\Delta)$ (energy W_0) and a second wave function $\Psi_E(^1\Delta)$ (energy W_E) :

$$\left.\begin{aligned}\Psi_0(^1\Delta) &= (1/\sqrt{2})\{|0\bar{0}1\bar{1}| \pm |0\bar{0}\ -1\ -\bar{1}|\}\\ \Psi_E(^1\Delta) &= (1/2)\{|0\bar{0}1\ -\bar{3}| + |0\bar{0}\ -3\bar{1}| \pm (|0\bar{0}\ -1\bar{3}| + |0\bar{0}3\ -\bar{1}|)\}\end{aligned}\right\} \quad . \quad . \quad . \quad (1.3)$$

where $$|0\bar{0}1\bar{1}| \equiv \text{det.}\{\phi_0(1)\overline{\phi_0(2)}\phi_1(3)\overline{\phi_1(4)}\}$$

Spin β is denoted by a bar in (1.3). Using the matrix components

$$\int \phi_m^* V \phi_{m+4} d\tau = \int \phi_m^* V \phi_{m-4} d\tau = -a;\ m = 0, \pm 1 \quad . \quad . \quad . \quad (1.4)$$

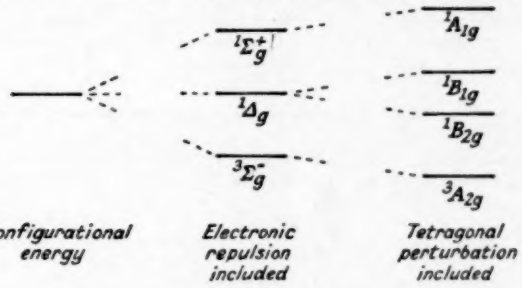
we can show that the splitting makes Ψ^- the more stable state. In this approximation the magnitude of the splitting is

$$W^+ - W^- = \{8a/(W_E - W_0)\}\iint \phi_1^*(1)\phi_{-1}(1)\{e^2/r_{12}\}\phi_1^*(2)\phi_3(2)d\tau_1 d\tau_2 \quad . \quad . \quad (1.5)$$

Ψ^+ and Ψ^- must now be classified in group $\mathbf{D_{4h}}$, in which they transform like $^1B_{1g}$ and $^1B_{2g}$ respectively. Schematically the result is shown in the third column of Fig. 1.

FIG. 1.

The circular field states of the lowest electronic configuration of cyclo*butadiene* (schematic).



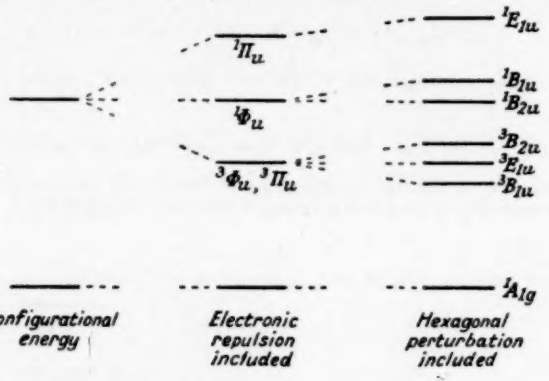
In benzene, the simplest normal aromatic compound, a similar calculation leads to the scheme in Fig. 2.

Figs. 1 and 2 may be taken as representative of the monocyclic members of the two classes of molecule; to bring out the essential differences between them it is necessary to refer to the conventional description of π-electron systems by structures with alternate single and double bonds. In empirical methods such structures are the reference points for the resonance energy which, in a widely understood sense, measures the π-electron energy over and above that of the most stable structure. For the sequel it is important to note that what is meant by a structure is not the same in the two empirical methods. In the valence-bond method a structure describes the (covalent) pairing of electrons one from each centre, whereas in the molecular orbital method a structure gives only part of the total weight to a covalent pairing scheme and the rest to dipolar bonds. This difference of reference point, together with other differences, is allowed for in the empirical parameters which are settled in each method from experimental results and normally therefore causes no difficulty. However, in a theory in which the form of wave functions is not rigidly specified, a single structure may, indifferently, be taken to have any one of a number of different wave functions (*viz.*, any mixture of covalent and polar constituents), and to these different energies must be assigned; so that in such a theory the resonance energy, which has to be measured relative to the energy of a structure, is not a well-defined quantity. Some progress may, however, be made by concentrating attention on another manifestation of the resonance phenomenon. The structures **A** and **B** of *cyclo*butadiene (Fig. 3), which provide the starting point for conventional resonance energy discussions, have physical significance only as combinations (**A** + **B**) and (**A** − **B**), each of which transforms like an

irreducible representation. One combination is more stable, and the other less stable, than the single structures **A** and **B** and the splitting between them is a fundamental measure of the resonance interaction. Unlike the resonance energy, this resonance splitting retains its significance wherever the calculation, either empirical or non-empirical, is based on atomic orbitals, and it therefore provides a link between the empirical and the non-empirical theory.

FIG. 2.

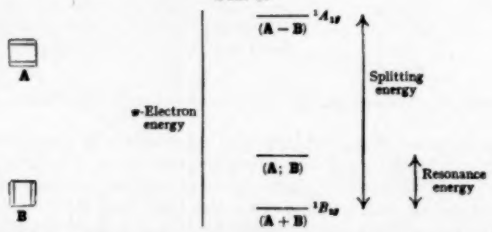
The circular-field states of the lowest and next-to-lowest configuration of benzene (schematic).



The splitting may (as in benzene) be identified with a spectroscopic interval and so is in principle an observable quantity.

It is readily found that, in *cyclo*butadiene, the two combinations (**A** + **B**) and (**A** − **B**) transform, respectively, like B_{2g} and A_{1g} of group $\mathbf{D_{2h}}$, the former being the more stable; whereas

FIG. 3.



in benzene the states are A_{1g} and B_{2u} of group $\mathbf{D_{6h}}$, the former again being the more stable. Reference to Figs. 1 and 2 now shows an important difference. Although in *cyclo*butadiene the two states arise in the same configuration of the circular field model, yet in benzene they arise in two different configurations. Evidently, therefore, the calculation of these intervals in the circular field model, or some elaboration of it, involves different physical effects. In *cyclo*butadiene the splitting is determined solely by electronic repulsion; in benzene, on the contrary, it is principally determined by terms in the energy measuring nuclear attraction, with a smaller modifying contribution by electron repulsion. Now in the valence-bond theory the splitting is in both cases given as a multiple of the exchange integral α. From these considerations it appears quite improbable that the same value of α can be applicable to both; more specifically, a value of α found by comparing theory and experiment in the $A_{1g} - B_{2u}$ interval of benzene (even if indirectly, *i.e.*, from the resonance energy) will be inapplicable to the $B_{2g} - A_{1g}$ interval of *cyclo*butadiene. This contention will be supported in more detail on p. 3181, where it will be shown that α for *cyclo*butadiene ought to be taken much smaller than that for benzene. In other words, the use in *cyclo*butadiene of an exchange integral appropriate

to benzene grossly exaggerates resonance effects: the mere possibility of writing a variety of structures has no clear energetic significance in this case, and the analogy with benzene that such a possibility suggests is an incorrect one. Indeed from Figs. 1 and 2 it seems that the proper analogy for the $B_{2g} - A_{1g}$ interval of *cyclo*butadiene is, not the $A_{1g} - B_{2u}$ interval of benzene, as the valence-bond theory makes it, but the $B_{2u} - E_{1u}$ interval.*

Diagrams like those in Figs. 1 and 2 may be constructed for the bigger monocyclic molecules. For systems of $4n + 2$ electrons the situation is essentially that of Fig. 2, and for $4n$ electrons that of Fig. 1; and the argument applies to these systems without essential change. The effect of distorting a monocyclic system to the corresponding dicyclic one is discussed quantitatively in §3 in the simplest case of *bicyclo*butadiene. In general terms, the distortion destroys the orbital degeneracy of the $4n$ electron systems in the sense of stabilizing the A_{1g} state (Fig. 1) relative to what, in the $4n$ electron case, is the B_{2ng} state. The interval $A_{1g} - B_{2ng}$ (which becomes $A_g - B_{1g}$ in group $\mathbf{D}_{2h}$, to which the distorted structures belong) is thus reduced from its monocyclic value. In the extreme case of *bicyclo*butadiene the interval is halved; but even here the energy level scheme remains closely related to that of the monocyclic molecule, making it clear that, where the molecules have the symmetry axis in (*b*) on p. 3175, the fundamental distinction remains between the peripheral systems of $4n$ π-electrons, which are examples of *pseudo*aromatic structures, and those of $4n + 2$ electrons, which are normal aromatic structures, whether the systems are monocyclic or not.

2. *Aromatic and* pseudo*Aromatic Compounds.*—It is important to be able to distinguish in a more general way between molecules which may be expected to show normal aromatic behaviour and those, like *cyclo*butadiene, which will not. As developed in this paper the distinction, while fundamentally one of energetics, may be based on symmetry properties in molecules having a certain minimum of symmetry in their molecular framework: the necessary element of symmetry is an axis passing through two or more π-electron centres, as possessed by the molecules illustrated and specified on p. 3175 and by more complex molecules such as pyrene (X). Molecules of lower symmetry cannot be classified in this way, and could be dealt with only by an actual calculation of energy levels.

A convenient starting point is the observation that, first, the π-electron system is abnormal where the ground state is non-totally symmetrical (cf. Fig. 1), and, secondly, that the valence-bond theory enables the ground-state symmetry to be correctly predicted. It should be possible therefore to identify the abnormal molecules in valence-bond theory, even though their energy levels cannot be calculated from it. Essentially this is a question of finding the symmetry properties of sums of sets of structures which, like the two Kekulé or the three Dewar structures of benzene, may be mutually transformed by the molecular symmetry operations.† This may

(VI)

(VII)

(VIII)

be reduced to a simple formula. The molecule is labelled (alternately as far as possible) with equal numbers of spin symbols α and β, in such a way as to give opposite spins to the ends of the double bonds of one Kekulé-like structure. Examples are (VI)—(VIII). A symmetry operation which transforms one structure into another of the same canonical set is characterized by two numbers p and q (cf. Craig, *Proc. Roy. Soc.*, 1950, *A*, **200**, 390): p is the number of interchanges of π-electron centres effected by the operation, and q is the number of interchanges of spin symbols required to restore the original labelling scheme from the transformed one.

It may be shown under the assumption in the footnote † below for unstarrable molecules,

* This is supported in so far as the experimental interval $B_{2u} - E_{1u}$ in benzene is 2·1 ev and the calculated $B_{2g} - A_{1g}$ interval of *cyclo*butadiene is 2·3 ev (p. 3181).

† In systems which are starrable in the terminology of Coulson and Rushbrooke (*Proc. Camb. Phil. Soc.*, 1940, **36**, 193), it may be proved that the most stable state is that in which mutually transforming structures are combined as the sum. In unstarrable molecules (many of which are also abnormal in our sense) there may occur structures whose difference combinations are the more stable. It may be shown, however, that these must always be structures of a high degree of excitation, and so probably not influential in the ground state wave function. Strictly, it must in this case be assumed that the most stable state is that which includes the most stable combination of the Kekulé-like structures, *i.e.*, those having the maximum possible double bonds.

but otherwise without restriction, that the character (χ) of the transfomation of the valence-bond ground state by this operation is

$$\chi = (-1)^{p+q} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2.1)$$

For example, the valence-bond ground state of pentalene is, from (2.1), antisymmetric ($p + q = 3$), and those of naphthalene and acenaphthylene are symmetric ($p + q = 4$, and 6), to the two-fold rotations about axes through the central atoms.

The argument in §1 applied to molecules in which the π-electron centres lie upon a simple closed curve, and it is at once clear that the circular field model cannot be applied, except very artificially, to molecules with interior π-election centres such as acenaphthylene (VIII). The valence-bond method, at least formally, is not limited in this way, and the ground state symmetry may in all cases be studied by applying (2.1). This suggests that the classification into normal and abnormal aromatic structures, according as $p + q$ is, or is not, even for all symmetry operations, may be extended to all cyclic conjugated systems having the necessary element of symmetry, and that it is not simply a matter of the *number* of π-electrons. It suggests, for example, that acenaphthylene and pyrene are to be classed as normal, even though they have 12 and 16 electrons respectively, and that molecules (XI) and (XII) with 10 and 14 π-electrons are abnormal.

(IX)

(X)

(XI)

(XII)

It must be emphasized that the extension of the argument to molecules with interior π-electron centres, while perhaps suggestive and plausible, rests primarily on analogy with the peripheral case. There are, however, no obvious exceptions, and it seems proper, therefore, to make the division of cyclic conjugated hydrocarbons into normal and *pseudo*aromatic depend on the symmetry of their most stable states as given by the relation (2.1). Molecules with totally symmetrical ground states are thus classified as normal aromatic, and those with non-totally symmetrical ground states as *pseudo*aromatic.

3. *Quantitative Discussion of the* 4*-Electron System.*—It is possible to give a quantitative account of the 4-electron system and so to give substance to the general considerations of §1. The results of a non-empirical calculation of the states of *cyclo*butadiene (Craig, *Proc. Roy. Soc.*, 1950, *A*, **202**, 498) differ from those of Fig. 1 mainly because the effect of the four point charges, treated in Fig. 1 as a simple tetragonal perturbation, is in fact so large that interactions between different LCAO configurations have to be considered. The method is to use $2p\pi$ LCAO configuration wave functions as the elements in a variation calculation, with energy terms found by computation from Slater $2p\pi$ atomic orbitals. A necessary test of the method may be made by comparing its results in benzene with experimental spectroscopic intervals, as in Table I.

TABLE I.

Calculated and experimental intervals in benzene.

(Parr, Craig, and Ross, *J. Chem. Physics*, 1950, **18**, 1561.)

	Calc.	Obs.		Calc.	Obs.
$^1E_{1u}$	9·9 ev	7·1 ev	$^3B_{1u}$	4·1 ev	3·8 ev
$^1B_{2u}$	4·4	4·9	$^1A_{1g}$	0	0

Two of the intervals agree with experiment to within 0·5 ev, while the calculated $A_{1g} - E_{1u}$ interval is too great. This is connected with the fact that the $^1E_{1u}$ state has a purely polar wave function: the restriction to $2p\pi$ atomic orbits in the LCAO wave functions exerts a large and specific effect in such states, and the method regularly makes them relatively too unstable. Hence, in discussing actual magnitudes by this method it is necessary to use calculated values for predominantly covalent states only, such as the last three in Table I. The states of *cyclo*butadiene (see Fig. 3) are of this type. The approximation used in *cyclo*butadiene (Table II) is the same as that in benzene.

The interval $B_{2g} - A_{1g}$ is the one which, according to the argument given in §1, measures the resonance splitting. Its value here is 2·5 ev. Now in valence-bond theory the interval is 4α and, α being given its spectroscopic value 1·92 ev (derived from benzene), this comes to 7·7 ev. Broadly, therefore, it may be deduced that valence-bond theory exaggerates by about three times the resonance splitting in *cyclo*butadiene. This may be taken as general support

TABLE II.

The low states of cyclo*butadiene.*

	Non-empirical	Valence-bond		Non-empirical	Valence-bond		Non-empirical	Valence-bond
$^1A_{1g}$	2·5 ev	7·7 ev	$^3A_{2g}$	0·7 ev	3·8 ev	$^1B_{2g}$	0 ev	0 ev

for §1. Furthermore, since the valence-bond theory makes the resonance energy also depend on the same exchange integral α, we should have to argue that the valence-bond resonance energy for *cyclo*butadiene—32 kcals./mole—is also too great by a factor of 3, and that the valence-bond value ought to be about 11 kcals./mole. Our procedure would then have been to determine α for *cyclo*butadiene by using the non-empirical calculation of the splitting energy and comparing this with the valence-bond calculation of the same quantity. A non-empirical calculation of the resonance energy itself is not possible for reasons discussed in §1.

*cyclo*Butadiene is not, of course, a general representative of the molecules (I)—(IV). The others are structures with two or more rings, being distorted to $\mathbf{D}_{2h}$ symmetry by cross links. A structure which, in the four-electron case, more closely imitates the features of higher members is *bicyclo*butadiene (V), and in the detailed calculations to be described attention is centred on the π-electrons in this hypothetical molecule.* For this, as for the larger molecules (II)—(IV), both empirical methods give large resonance energies, but disagree as to the symmetry of the ground states. It is necessary only to describe the calculations by the non-empirical method briefly. The calculations for *cyclo*butadiene have been set out fully (*loc. cit.*), and the modifications required for *bicyclo*butadiene are obvious.

The representations of $\mathbf{D}_{4h}$ (for *cyclo*butadiene) correlate with those of $\mathbf{D}_{2h}$ (for *bicyclo*butadiene) as follows. A_{1g} and B_{1g} of $\mathbf{D}_{4h}$ both transform like A_g of $\mathbf{D}_{2h}$; and A_{2g} and B_{2g} of $\mathbf{D}_{4h}$ both transform like B_{1g} of $\mathbf{D}_{2h}$. Further, the orbitals ϕ_0 and ϕ_2 of *cyclo*butadiene belong to the representation B_{1u} of $\mathbf{D}_{2h}$, whereas $\phi_{\pm 1}$ splits into components transforming like B_{2g} and B_{3g}. Proceeding in a conventional way, the non-empirical calculation is based on the following molecular orbitals: †

$$\zeta_1 = 0{\cdot}527\{(a + c) + 0{\cdot}378(b + d)\} \qquad \zeta_3 = 0{\cdot}822(a - c)$$
$$\zeta_2 = 0{\cdot}753\{0{\cdot}627(a + c) - (b + d)\} \qquad \zeta_4 = 0{\cdot}721(b - d)$$

in which the labels a, b, c, and d are those of the $2p\pi$ orbitals on the four carbon atoms of *bicyclo*butadiene (V), the bond a—c being taken as shorter than b—d. The complete set of configurational wave functions may now be written, and their energies expressed in integrals over molecular orbitals. These may be expanded into integrals over atomic orbitals and so evaluated analytically as described for benzene (*loc. cit.*). To secure consistency with the calculations of benzene and *cyclo*butadiene, three- and four-centre integrals are used as well as integrals which are accurately known, and the method for approximating them is that of Sklar (*J. Chem. Physics*, 1939, **7**, 984). When secular equations are solved to allow for configurational interaction, the results in Table III are obtained; ϵ_1 and ϵ_2 are the energies of the orbitals ζ_1 and ζ_2. The interval $^1B_{1g} - {}^1A_g$ in conventional valence-bond theory is 3·8 ev. The resonance splitting is now less than one-half of that found in *cyclo*butadiene itself, and so very small compared with expectations based on supposed analogies with normal aromatic compounds. The splitting is,

* It is the more necessary to consider in detail the effect of this distortion because the molecular orbital theory finds either zero (*cyclo*butadiene), or small, resonance energies in monocyclic molecules with $4n$ π-electrons, and so at first sight deals with this case fairly well. But it finds quite large resonance energies in, for example, dicyclic molecules, and so makes the cross-links an important stabilizing influence. This proposition can most simply be tested as described in the text.

† These molecular orbitals diagonalize the "core" energy matrix, *i.e.*, the matrix of the energy of an electron in the field of four carbon ions. By their use some troublesome non-diagonal terms in the total energy are avoided, but any complete set of LCAO $2p\pi$ molecular orbitals will give the same final results.

again, somewhat less than one-third of that calculated in valence-bond theory, and the effect of the cross-linking bond is to reduce the resonance energy (cf. §1).

TABLE III.

State	π-Electron energy, ev.	Excitation energy, ev.
^1A_g	$2\varepsilon_1 + 2\varepsilon_2 + 57{\cdot}5$	1·0
$^3B_{1g}$	$2\varepsilon_1 + 2\varepsilon_2 + 57{\cdot}5$	1·0
$^1B_{1g}$	$2\varepsilon_1 + 2\varepsilon_2 + 56{\cdot}5$	0

4. *Conclusion.*—The purpose of previous sections has been to establish that the resonance phenomenon in conjugated molecules, whether conceived in terms of hypothetical resonance structures or in molecular orbitals, occurs strongly only when certain additional conditions are met. It so happens that other possible cyclic conjugated molecules in which these conditions are violated are not yet known. Analogies between these and normal aromatic compounds, made either qualitatively, or implied by the use of simple π-electron theories, take no account of the special features of these exceptional molecules, and seem likely therefore to be incorrect.

In order to bring out the differences from normal aromatic compounds in their most cogent form, the *pseudo*aromatic compounds have been supposed to have equal bond distances of 1·40 Å. However, even this configuration is not associated with large resonance stabilization; and it is not therefore expected to be that in which actual molecules would be found. For, if resonance is not important, the more stable configuration is that in which the bonds are alternately long and short: the short bonds allow more favourable π-binding, and the long (single) bonds allow less unfavourable repulsions between π-electron pairs. *pseudo*Aromatic compounds therefore might be expected to show marked alternation in bond length.

This is of some interest in connection with *cyclo*octatetraene. Now this compound is not flat, and this takes it formally beyond the scope of the present investigation. If, however, the ideas of this paper are correct, it will be clear that no large π-stabilization is to be associated with a flat model with equal bond distances, and therefore that the loss of such π-stabilization is a less important structural influence than would be expected were the molecule benzenoid. The probable configuration, as described from *X*-ray measurements by Kaufman, Fankuchen, and Mark (*Nature*, **1948**, **161**, 165), has alternate long and short bonds and thus is compatible with, and may even support, these views. In interesting contrast to *cyclo*octatetraene, it is here implied that a molecule with two fused eight-membered rings, having fourteen π-electrons, would be a normal aromatic substance. In spite of non-planarity, π-electron resonance should be a structurally important feature, and should lead to definite physical differences from *cyclo*octatetraene as, for example, more nearly equal bond distances; in principle, and always supposing that transformation to the still more stable anthracene does not interfere, this would provide a test of this work.

The author has pleasure in thanking Prof. C. K. Ingold, F.R.S., and Dr. Allan Maccoll for discussions about this subject.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES, UNIVERSITY COLLEGE,
GOWER STREET, LONDON, W.C.1. [*Received, June 22nd,* 1951.]

699. *Separations by Partition Chromatography on Paper.* (i) *Strontium from Barium, Calcium, and Magnesium.* (ii) *Potassium, Rubidium, and Cæsium.* (iii) *Sodium and Lithium.*

By Christina C. Miller and Robert J. Magee.

A mixture of concentrated hydrochloric acid and *n*-butanol (95 : 5 by vol.), saturated with *n*-butyl chloride, has been used to separate strontium chloride from barium, calcium, and magnesium chlorides. Sodium rhodizonate has served for the detection and estimation of 2·5—500 μg. of strontium. 500 Micrograms of barium, calcium, magnesium, or any alkali metal did not interfere with the detection of 2·5 μg.

Potassium, rubidium, and cæsium chlorides (total weight of cations ≯1 mg.) have been separated by means of a mixture of concentrated hydrochloric acid, methanol, *n*-butanol, and *iso*butyl methyl ketone (55 : 35 : 5 : 5). For the detection and estimation of 5—1000 μg. of the three cations, the lead cobalt alkali hexanitrites have been formed. One mg. of sodium, lithium, calcium, strontium, barium, or magnesium did not influence the detection of the minimum amounts.

For the separation of sodium and lithium chlorides a mixture of methanol and *n*-butanol (4 : 1) has been used. In solutions containing a maximum of 500 μg. of any combination of the two cations, 2·5—500 μg. amounts of both have been detected and estimated in ultra-violet light as the fluorescent alkali zinc uranyl acetates; 500 μg. of potassium, rubidium, cæsium, calcium, barium, strontium, or magnesium did not influence the results.

In systematic qualitative analysis, in which the alkaline-earth metals and magnesium are commonly separated as a group, the certain detection of strontium in association with a large excess of barium is troublesome, since both metals react similarly with so many reagents. As a rule, barium is first removed by precipitation as chromate and the filtrate is examined for strontium. Unless great care is taken in effecting the precipitation a small amount of strontium may be completely retained by the barium chromate, or a small amount of barium may escape precipitation and subsequently be reported as strontium.

The systematic detection of the alkali metals, in the absence of all other cations, usually involves their separation into two sub-groups containing, respectively, potassium, rubidium, and cæsium, and sodium and lithium. Sodium and lithium chlorides can then be separated from each other by means of an organic solvent, *e.g.*, amyl alcohol, acetone, or pyridine. The separation of potassium, rubidium, and cæsium is by no means easy, the detection of a small amount of either of the first two in the presence of an excess of the others being particularly difficult.

Within the last few years some striking separations by partition chromatography on strips of filter-paper have been effected of metal ions whose detection in the presence of each other by orthodox chemical methods has been difficult. Some such new means were accordingly sought for facilitating especially the detection of a small amount of strontium in the presence of much barium, and the separation of the alkali metals from one another.

Separation of Strontium from Barium.—For the separation of calcium, strontium, and barium chlorides, which were said to be difficult to separate, Burstall, Davies, Linstead, and Wells (*J.*, 1950, 516) recommended pyridine containing 20% of water and 1% of potassium thiocyanate. We have failed to obtain good separations of barium and strontium by this method, barium invariably travelling down the paper like strontium. We paid particular attention to solvents that had been employed for ordinary chemical separations of barium and strontium salts, and first obtained successful indications when a mixture of butanol and concentrated hydrochloric acid (cf. Kallmann, *Anal. Chem.*, 1948, **20**, 449) was applied to the chlorides of barium and strontium. As a result of numerous experiments in which the proportions of these two components were varied, and freshly prepared and old mixtures were used, it was concluded that the best solvent was a mixture of *n*-butanol and concentrated hydrochloric acid (5 : 95 v/v), saturated with *n*-butyl chloride. With all the mixtures tried, barium was held near the original spot of deposition of the test solution whereas strontium, calcium, and magnesium travelled down the paper, magnesium moving the greatest, and

strontium the least distance. The proportion of acid in the mixture influenced the relative rates of travel of strontium, calcium, and magnesium, and the mixture selected gave the best separation of all three. The presence of *n*-butyl chloride almost entirely prevented slight "tailing" of barium and thus gave a cleaner-cut separation of barium and strontium, favouring the detection of small amounts of the latter in the presence of a large excess of the former.

For the detection of strontium, sodium rhodizonate could be used after the paper had been freed as far as possible from acid. The colour obtained with strontium, which could not be confused with that due to barium, ranged from orange with small amounts, through orange-red to purple-red for large amounts. Small amounts of barium gave bright pink patches, and large amounts, brilliant carmine. On strips of paper 1·5 cm. wide, 2·5 μg. of strontium were easily found and could be separated from 500 μg. of barium in experiments of 3½—4 hours' duration in which the solvent reached a line 20 cm. below the original spot of deposition of the test solution. The presence of 500 μg. of calcium or magnesium, or any alkali metal did not obviously influence the position of the band due to strontium, or prevent the detection of 2·5 μg. of the element.

Bands due to magnesium in quantities up to 500 μg. ended a short distance above the solvent front and were completely separated from those due to strontium. Bands due to calcium lay between those of strontium and magnesium, and the separation of small and moderate amounts of the three elements was considered to be complete. 500 Micrograms of calcium were separated from 2·5 μg. of strontium. There was probably a tendency for slight overlap of calcium and magnesium and of calcium and strontium to occur when, say, 250 μg. of each were present. This was of no significance for the detection and estimation of strontium, since the rhodizonate test for the latter did not require the complete removal of calcium. The positions of the bands due to 500 μg. amounts of the alkali metals were approximately as follows: That due to sodium extended from just below the starting line to a point more than half-way down the paper. That for lithium was separated by a short distance from that for sodium and reached probably to the solvent front. The bands due to potassium, rubidium, and cæsium were located mainly in the bottom half of the paper, cæsium probably reaching to the solvent front and being partly separated from rubidium, which was likewise partly separated from potassium.

Reasonable estimations of the amounts of strontium separated from mixtures could be made. Chromatograms prepared from quantities of strontium ranging from 2·5 to 500 μg. showed a useful gradation in colour intensity and area of the developed band on which estimations could be based. In experiments in which the solvent travelled 20 cm. beyond the starting line the positions of the bands with respect to the latter were as follows:

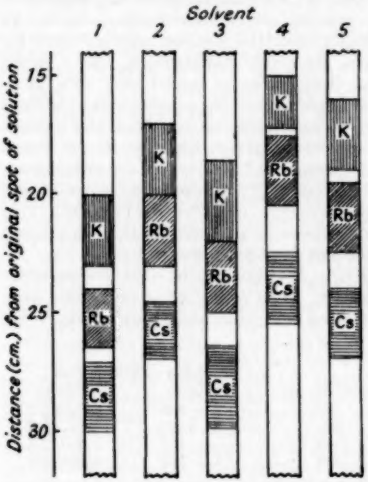
Amount of Sr (μg.)	2·5	5	10	25	50	100	250	500
Upper limit of band (cm.)	8·5	9·1	9·2	8·6	8·3	7·2	4·5	4·5
Lower limit of band (cm.)	11·0	12·3	12·7	13·0	13·6	13·4	13·4	14·0

Separation of Potassium, Rubidium, and Cæsium.—In ordinary chemical extraction work on the separation of the chlorides of potassium, rubidium, and cæsium, mixtures of ethanol and hydrochloric acid have been employed. Hillyer (*Ind. Eng. Chem., Anal.*, 1937, **9**, 236), for instance, recommended a mixture of concentrated hydrochloric acid and ethanol (1 : 2) for the separation of much rubidium chloride and cæsium chloride from a little potassium chloride. In all our preliminary work on neutral chloride solutions of the alkali metals in which partial separations were indicated, the solvents contained concentrated hydrochloric acid or hydrobromic acid together with an alcohol, a ketone, or tetrahydropyran, or mixtures of these. The destructive effect of hydrobromic acid on the dried paper rendered its use impracticable. Promising separations were given with solvents containing, in the main, methanol and concentrated hydrochloric acid. The results for 5 experiments in which solvent mixtures containing these as chief components were allowed to travel 50 cm. from the original spot of deposition of the test solution are shown pictorially in the figure. The composition of solvent No. 5 was chosen so as to incorporate the good features of solvents Nos. 1 and 4, which gave the best separations, respectively, between potassium and rubidium, and between rubidium and cæsium.

For the detection of the three elements the formation of complex hexanitrites containing lead and cobalt was found to be best, although their tinctorial power was not outstanding. All attempts to improve upon this aspect by employing salts other than those of lead and cobalt met with no success. On strips of paper 4 cm. wide, 5 μg. of potassium gave an easily detectable yellow stain, but 5 μg. of rubidium or cæsium gave a very pale yellow stain. Large amounts of potassium, rubidium, and cæsium gave orange-yellow, brownish-black, and orange-brown colours, respectively.

With solvent No. 5 it was possible, in experiments made at room temperature and lasting about 17 hours, to effect complete separation of potassium, rubidium, and cæsium in mixtures containing a minimum of 5 μg. of any of these elements and a maximum of 1 mg. of the combined elements. In one experiment on the separation of 5 μg. of rubidium from 500 μg. of each of potassium and cæsium the positions of the bands with respect to the starting line were: K, 19·6—28·9 cm.; Rb, 29·5—31·5 cm.; Cs, 32·8—36·5 cm. A separation of 10 μg. of potassium from 1 mg. of rubidium similarly gave: K, 24·4—27·1 cm.; Rb, 27·8—32·7 cm.

In all the separations obtained with the same solvent, the relative positions on the strips, with respect to each other, of the bands associated with small amounts of potassium, rubidium,



K = 100 μg.; Rb = 100 μg.; Cs = 50 μg.

Composition of solvents (parts by volume).

Solvent.	1.	2.	3.	4.	5.
Conc. HCl (*d* 1·18)	55	50	50	50	55
Methanol	40	40	40	40	35
n-Butanol	5	—	—	—	5
Tetrahydropyran	—	10	—	—	—
Methyl propyl ketone	—	—	10	—	—
*iso*Butyl methyl ketone	—	—	—	10	5

and cæsium, were reasonably constant, but, with respect to the solvent front, the bands might occasionally show an upward or downward displacement of a few cm. (R_F values not constant). If, therefore, a chromatogram showed a single band, one could, by merely calculating the R_F value, confuse potassium with rubidium or rubidium with cæsium. Similarly, if there were two bands near each other, potassium and rubidium could be confused with rubidium and cæsium. Two bands fairly far apart could only be attributed to potassium and cæsium. In examining a solution for potassium, rubidium, and cæsium the simplest way to ensure a correct interpretation is to take two portions and add to one a little cæsium chloride before preparing the chromatograms. The ratios of the R_F values of potassium and rubidium to that of cæsium, which is commonly about 0·7, are approximately 0·8 and 0·9.

The effect of some other metals on the detection of potassium, rubidium, and cæsium was investigated. One mg. of sodium, lithium, barium, calcium, strontium, or magnesium as chloride had no influence on the detection of 5 μg. of potassium, rubidium, or cæsium, or on the position of the bands, in experiments in which the solvent advanced 50 cm. beyond the original spot of deposition of the test solution. The band due to sodium stretched from the starting point to the 7 cm. mark, that of lithium occupied the same position as cæsium but tended to spread down the paper, barium was held mainly at the starting point but trailed somewhat to the 10 cm. mark, and the band due to strontium stretched from the starting point to the 20 cm. mark. Calcium and magnesium were found between 18 and 32 cm. and between 28 and 40 cm., respectively. Ammonium formed a complex hexanitrite like potassium, rubidium, and cæsium, 1 mg. giving a yellow-brown band almost coincident with that due to cæsium. It was important to exclude ammonia vapour at all stages in the preparation of the chromatograms.

The amounts of potassium, rubidium, and cæsium separated from mixtures could be estimated with reference to sets of chromatograms prepared for amounts of the various

elements ranging from 5 to 1000 μg. Whereas the band for potassium markedly lengthened, especially in an upward direction, as the amount of the element increased, the bands for rubidium and cæsium remained compact, as the following table shows:

Element, μg.		5	10	25	50	100	250	500	1000
Length of bands (cm.)	K	2·9	3·5	4·0	4·2	4·7	6·2	10·6	15·4
	Rb	2·5	2·8	2·6	2·7	3·0	4·1	5·1	5·4
	Cs	2·7	3·0	3·6	3·8	4·0	4·2	4·9	6·3

Estimations of potassium were related partly to intensity of colour but mainly to band length or area. Intensity of colour was of more importance in estimating rubidium and cæsium.

Separation of Sodium and Lithium.—Burstall *et al.* (*loc. cit.*) used methanol for the separation of 100 μg. amounts of sodium, lithium, and potassium present as neutral chlorides. Although we obtained separations of sodium and lithium chlorides with the solvent mixture used for potassium, rubidium, and cæsium, the bands were not altogether satisfactory. As a result of experiments with mixtures of alcohols it was found that methanol mixed with 25% of *n*-butanol gave better separations than methanol alone, especially when the proportions of sodium and lithium were widely varied. On strips of paper 1·5 cm. wide, down which the solvent was allowed to travel 20 cm. beyond the position of the test solution initially, it was found possible to separate 2·5 μg. of sodium from 500 μg. of lithium and *vice versâ*. A satisfactory means of detecting the elements was not easily found. Ultimately, we used a solution of zinc uranyl acetate which has been used recently by Pollard, McOmie, and Stevens (*J.*, 1951, 771) for the detection of sodium. With both sodium and lithium it gave bands that fluoresced brightly in ultra-violet light, the limit of detection of the elements being about 1 μg.

For the estimation of sodium and lithium on the strips, chromatograms were prepared for amounts of sodium and lithium ranging from 2·5 to 500 μg. The positions of the bands were found to lie within the following distances from the starting line, in experiments in which the solvent travelled 20 cm. beyond that point:

Element, μg.	Position of bands (cm.). Sodium.	Lithium.	Element, μg.	Position of bands (cm.). Sodium.	Lithium.
2·5	5·9—7·6	16·0—17·2	50	4·2— 8·6	13·2—17·2
5	5·5—7·7	15·5—17·4	100	3·3—10·0	12·3—17·3
10	4·5—8·5	14·5—17·4	250	2·1— 9·5	11·0—17·3
25	5·8—9·2	13·5—17·5	500	1·7— 9·9	9·2—17·7

The area of the fluorescent patch was used as the basis for estimations of quantity.

The influence on the detection of 2·5 μg. of sodium or lithium of 500 μg. of each of the other alkali metals, alkaline-earth metals, and magnesium, as chlorides, was found to be inappreciable. The positions occupied by the various elements on strips down which the solvent had travelled 20 cm. from the starting line were as follows: The bulk of potassium, rubidium, and cæsium remained on the original spot of deposition but some trailed down for about 4·5 cm. The bands due to barium, strontium, calcium, and magnesium lay between 1 and 8 cm., 1 and 13 cm., 4 and 14 cm., and 13 and 17 cm., respectively.

Experimental.

The chromatographic apparatus used for 2—4 hour experiments was similar to that employed by Burstall *et al.* (*loc. cit.*), except that the glass gas-jars which had a ground flange were inverted over sheets of plane glass, and the glass boats (5 ml. capacity) were sealed to short pillars of glass that were inserted into hollow, upright stems sealed on to glass tripods. Boats could thus be interchanged and their heights adjusted to suit the various gas-jars. For the long experiments the apparatus consisted of a glass cylinder (internal diameter 19 cm.) with ground flanges at top and bottom, which rested on a ground-glass plate and was surmounted by a bell-jar so as to give a total height of 70 cm. Within was a glass boat (length 12 cm., capacity 60 ml.) provided with the usual glass supports for the paper. To the boat were sealed 4 short limbs that could be inserted into upright glass tubes fitted into rubber bungs to provide a firm support. From the boat four paper strips could be hung. No special arrangements were made for maintaining constancy of temperature, which was usually between 12° and 15°; even during the long experiments the maximum range was less than 5° and no sharp changes occurred.

All the experiments were made on strips of Whatman No. 1 filter-paper cut 1·5 cm. wide and 30 cm. long for short runs, and 4 cm. wide and 67 cm. long for long runs. Pencil lines were ruled 2·5 and 7·5 cm. from the ends of short strips, and 7 and 10 cm. from those of long strips. Neutral solutions of metallic chlorides were used throughout, small amounts being placed, as indicated later, just below the first lines.

The boats and, unless otherwise stated, beakers at the foot of the chromatographic apparatus were charged with freshly prepared solvent mixture about 1 hour before the insertion of paper strips, which were so placed that the upper ends dipped into the boat and the parts between the two marks hung vertically.

The solvents used were fractionated *n*-butanol, methanol (obtained from James Burrough, Ltd., London, and redistilled), AnalaR hydrochloric acid (*d* 1·18), and *n*-butyl chloride and *iso*butyl methyl ketone (both from British Drug Houses) which were used as received.

For spraying, the strips were held taut and a simple atomiser actuated by a current of compressed air was employed.

Procedure for Strontium.—The solvent mixture was hydrochloric acid and *n*-butanol (95 : 5 by vol.), saturated at room temperature with *n*-butyl chloride. Experiments were made on short strips of paper with 0·01 ml. of test solution containing a maximum of 500 μg. of cations, added a little at a time from a capillary pipette so that the diameter of the spot was >1 cm. The prepared strip was left on an improvised glass hot-plate (40°) for 5 minutes in order to ensure thorough drying which was essential for satisfactory separations, and then placed within the gas-jar. The solvent was allowed to travel down the paper to the second mark (time 3½—4 hours), then the strip was removed, hung upside down a short distance from a steam radiator (35—40°), and left until dry (30 minutes) and reasonably free from acid. Further treatment with ammonia vapour was required before stable colours could be obtained with sodium rhodizonate. For this purpose the strips were hung for 10 minutes on a frame within a bell-jar under which was a dish of concentrated ammonia.

Finally, the strip was sprayed with a saturated aqueous solution of sodium rhodizonate mixed with 25% of methanol, held above the hot-plate for a minute in order to dry up the bulk of the liquid, and then left in the air to dry completely. The colour did not deteriorate on standing and could be compared at leisure with a previously prepared set of standards.

Detection and Estimation of Calcium and Magnesium.—The presence of calcium and magnesium on the strips was readily shown by spraying them with a solution of 8-hydroxyquinoline (5% in a mixture of methanol, chloroform, and water, 85 : 10 : 5) before the application of sodium rhodizonate, and then exposing them to ammonia vapour for a minute before placing them in ultra-violet light. Greenish-yellow fluorescent bands were observed, 5 μg. of each metal being detectable. The lengths of the bands increased with increasing amounts of the elements, and sets of standards were prepared. Unfortunately, they deteriorated rapidly on standing. If this difficulty were overcome there is little doubt that calcium, magnesium, and strontium could be detected and estimated on the same strip, because the subsequent detection and estimation of strontium by means of sodium rhodizonate were unaffected by the prior spraying with 8-hydroxyquinoline.

Procedure for Potassium, Rubidium, and Cæsium.—The solvent mixture, hydrochloric acid, methanol, *n*-butanol, and *iso*butyl methyl ketone (55 : 35 : 5 : 5 by vol.), was placed only in the boat. The dish at the foot of the chromatographic outfit was charged with concentrated hydrochloric acid, which prevented the bands associated with much potassium trailing back to the starting point. 0·02 Ml. of test solution was very carefully placed as a narrow band on a long paper strip by drawing the fine tip of the pipette quickly across the paper from a point 5 mm. in from one edge to within 5 mm. of the other edge. The strip was hung in air for 15 minutes, intensive drying over a hot-plate not being permissible because it subsequently caused unsatisfactory movement of potassium. The strip was placed as usual in the chromatographic apparatus and left until the solvent had travelled 50 cm. from the starting line (about 17 hours). After removal from the apparatus, the strip was hung upside down near a steam radiator until as free as possible from acid and then held horizontally for spraying.

Detection of the Bands.—The production of complex hexanitrites was very satisfactory. While this work was in progress Beerstecher (*Analyt. Chem.*, 1950, **22**, 1200) recommended the use of a reagent prepared from lead and cobalt nitrates and sodium nitrite. Our final reagent was of the same composition as that mentioned by Behrens-Kley ("Mikrochemische Analyse," Voss, Leipzig, 1921, p. 28), except that copper acetate was replaced by cobalt acetate. It was prepared by dissolving hydrated cobalt acetate (11·4 g.), hydrated lead acetate (16·2 g.), sodium nitrite (20 g.), and glacial acetic acid (2 ml.) in water (150 ml.). The acetate buffered the small amount of hydrochloric acid retained by the paper. For spraying purposes the centrifuged solution was mixed with 25% of methanol. A light initial spray usually served to show the number of bands, but spraying had to be continued until colour development was a maximum. It was, however, important not to spray until the strips were wet. Since the reagent solution was yellow, an excess gave a yellow background to the bands and tended to obscure faint bands. By suspending the sprayed strips in a cylinder of cold water and moving them gently up and down for not more than 5 minutes we effectively removed this background, but slight solution of the complex nitrite of cæsium occurred so that the detection of 5 μg. was less certain. The bands due to potassium and rubidium were unaffected. The washed strips were afterwards hung in front of a radiator to dry, and the positions of the bands noted. The colours were stable.

Procedure for Sodium and Lithium.—The solvent mixture contained methanol and *n*-butanol (4 : 1 by vol.). 0·01 Ml. of test solution was placed in a thin line across a 1·5-cm. strip, but without reaching to the edges. The strip was left to dry in air, then placed in the chromatographic apparatus, and the solvent allowed to travel 20 cm. beyond the starting line (time about 100 minutes). On removal from the gas-jar the strip was left to dry in air and then sprayed from the bottom up with zinc uranyl acetate solution (Barber and Kolthoff, *J. Amer. Chem. Soc.*, 1928, **50**, 1625) to which 25% of methanol had been added. The air-dried sprayed strip was examined under ultra-violet light and compared, if desired, with standards. Sodium and lithium were still detectable on strips that had been kept for 3 months.

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CHEMISTRY DEPARTMENT,
KING'S BUILDINGS, EDINBURGH.

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700. *Qualitative Semimicro-analysis with Reference to Noyes and Bray's System: Analysis of the Combined Alkaline-earth and Alkali Groups.*

By Christina C. Miller and Robert J. Magee.

A scheme of analysis is presented for the detection and approximate estimation of 0·1—20 mg. of barium, calcium, strontium, magnesium, sodium, lithium, potassium, rubidium, and cæsium in mixtures containing a maximum of 20 mg. of these cations in 0·4 ml. of solutions of their chlorides. In separate portions barium, magnesium, and cæsium are detected and estimated by means of potassium chromate, *p*-nitrobenzeneazoresorcinol, and potassium tetraiodobismuthate, respectively. From a fourth portion calcium is extracted by means of concentrated nitric acid and converted into calcium sulphate. Three further portions are submitted to different chromatographic separations on paper. In one, strontium is identified as its rhodizonate, in another, the fluorescent sodium and lithium zinc uranyl acetates are formed, and, in the last, the hexanitrites of potassium, rubidium, and cæsium with lead and cobalt are produced.

Schemes for the analysis on a semimicro-scale of nine groups of Noyes and Bray's system ("A System of Qualitative Analysis for the Rare Elements," Macmillan, New York, 1927) have already been published by Miller and Lowe (*J.*, 1940, 1258, 1263) and Miller (*J.*, 1941, 72, 786; 1943, 72; 1947, 1347). This paper describes the further application of semimicro-analytical methods to the combined alkaline-earth and alkali groups, which have already been analysed separately on a micro-scale by Benedetti-Pichler and his co-workers (*Ind. Eng. Chem., Anal.*, 1939, **11**, 117; 1938, **10**, 107), whose procedures do not markedly differ from those of Noyes and Bray. Within the past decade, numerous schemes of semimicro-analysis of varying merit have been given for the alkaline-earth metals and for a group containing magnesium, potassium, and sodium, and perhaps lithium.

In Noyes and Bray's scheme the solution left after the removal of metals precipitable with ammonium sulphide may contain barium, calcium, strontium, magnesium, sodium, lithium, potassium, rubidium, cæsium, and ammonium salts, partly as perchlorates. By evaporation of the solution to dryness and moderate ignition in the presence of ammonium chloride, perchlorate is destroyed, and finally ammonium salts are eliminated. Provision can also be made for the removal of sulphate, so that eventually a solution of metal chlorides is obtained. Noyes and Bray and Benedetti-Pichler separated the metals into two groups and then systematically separated their components from one another.

Our efforts to simplify and improve the detection and estimation of the various elements by orthodox chemical methods have met with but limited success, and only for barium, magnesium, cæsium, and calcium are simple direct tests prescribed. The partition chromatographic separations on filter-paper (see preceding paper) for strontium, sodium, lithium, potassium, rubidium, and cæsium, have, however, enabled us to complete an extremely simple scheme for the detection of all the metals named, within the limits set forth in the summary.

Experimental.

Preparation of the Group for Analysis.—Neutral solutions containing chlorides of the various metals, and free from ammonium salts, were prepared from the purest materials obtainable.

Alkaline-earth and Alkali Groups. (The figures in parentheses are referred to in "Notes on Methods and Tests.")—*Solution* (0·4 ml.). Contains barium, magnesium, cæsium, calcium, strontium, sodium, lithium, potassium, and rubidium chlorides. Test separate portions as follows:

(*a*) Test 0·02 ml. for Ba in a fine-tapered centrifuge cone. Add 2N-acetic acid (0·02 ml.) and 3N-ammonium acetate (0·04 ml.), heat to boiling, and add *very gradually*, with continuous stirring, 1·5M-potassium chromate (0·01 ml.). A yellow precipitate shows *barium*. Reheat to b. p., cool, centrifuge, and determine (1).

(*b*) Test 0·005 ml. for Mg in a 1-ml. centrifuge cone. Add 2N-hydrochloric acid (0·05 ml.), 0·4M-calcium chloride (0·15 ml.), and 0·1% *p*-nitrobenzeneazoresorcinol in 50% ethanol (0·05—0·2 ml.). Stir well and add 2N-sodium hydroxide (0·15 ml.). Again stir, then centrifuge and wash the precipitate with water. A blue colour in the precipitate shows *magnesium*. Compare with standards and a blank (2).

(*c*) Test 0·1 ml. for Cs in a centrifuge cone (2—3 ml.). Evaporate to dryness in a current of air, cool, and dissolve the residue as far as possible in water (0·025 ml.). Add *slowly* down the side of the

tube potassium tetraiodobismuthate reagent (0·05 ml.). Allow to mix, stir thoroughly, and, if the original residue has not dissolved completely, add more water (0·025 ml.). Finally, add more reagent, if required, until precipitation is complete. A brick-red, crystalline precipitate shows *cæsium*. Transfer to a fine-tapered cone for determination (3).

(*d*) Test 0·1 ml. for Ca in a centrifuge cone (2—3 ml.). Evaporate to dryness in a current of air in a heating block at 120—140°, add 0·1 ml. of nitric acid (*d* 1·42), and re-evaporate to dryness. Stir and break up the residue in more nitric acid (0·15 ml.), heat to boiling, and allow to cool. Centrifuge and repeat the extraction, if necessary. Evaporate the combined centrifugates to dryness as before, and take up the residue in water (0·08 ml.) and acetone (0·15 ml.), dissolving it as far as possible. Finally, add 0·01 ml. of concentrated sulphuric acid, stir well, and set aside for 5 minutes. If required, dissolve sulphates of metals other than calcium in more water (~0·05 ml.). A white precipitate remaining shows *calcium*. For determination, separate and wash the precipitate with acetone, then add 2N-ammonia (0·05 ml.) and 6N-ammonium carbonate (0·25 ml.). Boil for several minutes, cool, transfer to a fine-tapered cone, and compare with standards of calcium carbonate prepared *via* calcium sulphate (4).

(*e*) Test 0·01 ml. for Sr. Place the solution as a spot on a strip of Whatman No. 1 filter-paper, 1·5 cm. wide, dry, and insert the strip in a previously prepared chromatographic apparatus. Allow a mixture of hydrochloric acid (*d* 1·18) and *n*-butanol (95 : 5), saturated with *n*-butyl chloride, to travel 20 cm. down the paper from the starting line. For detection, spray with sodium rhodizonate solution. An orange- or purple-red band, one-third of the way down the paper, shows *strontium*, which is to be compared with standards (for full details see preceding paper).

(*f*) Test 0·01 ml. for Na and Li. Place the solution as a band on a strip of filter-paper, 1·5 cm. wide, dry, and insert the strip in a previously prepared chromatographic apparatus. Allow a mixture of methanol and *n*-butanol (4 : 1) to travel 20 cm. down the paper from the starting line. For detection, spray with zinc uranyl acetate reagent and examine in ultra-violet light. *Sodium* and *lithium* give fluorescent bands about one-third and two-thirds of the way down the paper, respectively, and may be determined with reference to standards (for full details, see preceding paper).

(*g*) Use two 0·02-ml. portions for K, Rb, and Cs, if test (*c*) has not been done. To one, add 0·001 ml. of 0·4M-cæsium chloride (~50 μg. of Cs). Place the solutions in bands on strips of filter paper, 4 cm. wide, and insert the latter in a previously prepared chromatographic apparatus. Allow a solvent composed of hydrochloric acid (*d* 1·18), methanol, *n*-butanol, and *iso*butyl methyl ketone (55 : 35 : 5 : 5) to reach a point 50 cm. from the starting line. For detection, use sodium lead cobalt nitrite reagent, which gives yellow bands with *potassium*, *rubidium*, and *cæsium*, the R_F values for K and Rb being ~80% and 90%, respectively, of that for Cs. Estimate by comparing with standards (full details are given in the preceding paper).

Notes on Methods and Tests.—The experimental technique has been described in earlier papers.

Note 1. This test was recommended by Noyes and Bray (*loc. cit.*) who covered a range of 0·5—500 mg. of barium in a final volume of 25 ml. Benedetti-Pichler, Crowell, and Donahoe (*Ind. Eng. Chem., Anal.*, 1939, **11**, 117) used the same reaction on one-thousandth of the scale. We found it desirable, in dealing with 0·005—1 mg. of barium, to have a final volume of ~0·1 ml. In a smaller volume, the maximum amount of strontium under consideration (1 mg.) might give a slight precipitate. If desired, one may dissolve a small chromate precipitate in hydrochloric acid, evaporate to dryness, and add sodium rhodizonate to the neutral solution of the residue. Barium and strontium rhodizonate are reddish-brown, but the former is partly converted, by treatment with a small quantity of 2N-hydrochloric acid, into a very characteristic carmine precipitate, whereas strontium rhodizonate is dissolved without colour-change.

Note 2. Newell, Pike, and Ficklen (*Z. anorg. Chem.*, 1935, **225**, 281) examined the effect on this well-known test of many other cations. Alkaline-earth metals, if present in high enough concentration, might give a hydroxide precipitate, which, however, neither adsorbed the reagent with colour change nor prevented its adsorption by magnesium hydroxide. Estimations of magnesium were adversely affected by the dispersal of the blue complex in variable amounts of precipitate. The addition to all the solutions to be compared of 2 mg. of calcium ions (those most likely to be precipitated), which is far in excess of the amount that could be present in the portion of the test solution used, gave an almost constant bulk of precipitate that permitted estimations to be made and did not prevent the detection of 1 μg. of magnesium in association with any other group component (250 μg.). 0·05 Ml. of the reagent was adequate for 1—50 μg. of magnesium, but more was required for larger quantities. A trace of sulphate present in the solution, if precipitated as barium sulphate, caused the final precipitate to assume a slight colour that might be attributed to the minimum amount of magnesium. Repetition of the test in the absence of additional calcium ions prevented misinterpretation.

Note 3. Benedetti-Pichler and Bryant (*Ind. Eng. Chem., Anal.*, 1938, **10**, 107) detected 5 μg. of cæsium as its iodobismuthate in the presence of 500 μg. of rubidium and potassium. Our reagent was prepared by slowly adding glacial acetic acid (25 ml.) to a suspension of bismuth oxide (1 g.) in saturated potassium iodide solution (10 ml.) (cf. Wenger, Duckert, and Rusconi, "Traité de Chimie Analytique Qualitative Minérale," Georg et Cie., Geneva, 1946, p. 284). In the prescribed test, the additional water was required to dissolve large amounts of sodium and lithium chlorides. Cæsium (25 μg.) was detectable alone and in association with any group component (5 mg.), except lithium, which raised the limit of detection to 50 μg.

Note 4. Rawson (*J. Soc. Chem. Ind.*, 1897, **16**, 113) strongly recommended the use of nitric acid (*d* 1·46) for separating soluble calcium nitrate from insoluble barium and strontium nitrates, but stated that for all ordinary purposes nitric acid (*d* 1·42) would suffice. Yagoda (*J. Amer. Chem. Soc.*, 1932, **54**, 984) used the method for separating calcium and lithium from strontium. We have found the

method excellent and very simple for separating calcium from barium and strontium, even in the presence of any alkali metal or magnesium. Potassium, rubidium, cæsium, magnesium, the bulk of the lithium, and some sodium accompanied calcium. Since it was important not to dilute the nitric acid used in the extraction, the amount of water of hydration left in the mixed nitrates had to be reduced to a low level, and appreciable breakdown of magnesium nitrate into magnesium oxide, which would liberate water on reaction with nitric acid, had to be avoided. With heating between 120° and 140° there was no evidence whatever that any significant amount of barium or >5 μg. of strontium ever went into solution.

The subsequent test for calcium had to be applied in the presence of a 200-fold excess of magnesium. The test given was recommended by Shvedov (abstracted in *Analyst*, 1949, **74**, 660), who found that acetone (60—80%) hindered the precipitation of magnesium sulphate and accelerated that of calcium sulphate. In order to precipitate calcium (25 μg.) quickly, the volume of solution was kept small initially, which meant that dissolution of the mixed nitrates in aqueous acetone might be incomplete and metallic sulphates other than calcium sulphate might separate out. The addition of a minimum of water, after the sulphuric acid, cleared up the solution excellently and left the calcium sulphate. It was essential to have the metals present initially as *nitrates*. Calcium (25 μg.) could be found in association with each of the other group components (5 mg.). Calcium sulphate was unsatisfactory as a basis for estimations, but calcium carbonate sufficed, provided that the standards were also prepared from calcium sulphate precipitates.

Analysis of Mixtures.—As a final test of the validity of the proposed scheme 14 mixtures of unknown composition were submitted to the junior author for full analysis. The results shown in the table are the estimated weights (in mg.) of the metals found. Where these differed from the weights taken the latter are shown in parentheses. Cæsium was first tested for by the chromatographic procedure in order that an unbiassed decision would be made. The results obtained thus are given *first* in the table.

No.	Ba	Ca	Sr	Mg	Na	Li	K	Rb	Cs
1.	0·2	0·2 (0·1)	0	4 (2)	0	0·1	0	0·2 (0·4)	0·1, 0·2 (0·2)
2.	2 (2·4)	4 (6)	1·2	0	0	0	0·15 (0·1)	15 (10)	0, 0
3.	10 (12)	0	0·15 (0·1)	0	0	1·6 (4)	0	0·1 (0·2)	0, 0
4.	0	0·1	2 (3)	0	4 (8)	0	0·8 (1·6)	1·5 (3)	0, 0
5.	0·4 (0·8)	0·2	0	0·8 (0·4)	0	2·4	6 (8)	0·2 (0·1)	5, 12 (9)
6.	0·1	20 (16)	0·15 (0·2)	0·1	0·2 (0·4)	0·1 (0·2)	0	0	0·2, 0·8 (0·8)
7.	0	0	0	3	0·4 (0·8)	0	0	20 (16)	0, 0·1 (0·1)
8.	16	0·1	0	0·1	0·1 (0·2)	0	0	0	0·8, 0·6 (0·4)
9.	0	0·2 (0·4)	3 (9)	0	0·1 (0·1)	0·4	5	0	5, 2 (5)
10.	0·4	0	0·2	0·4 (0·8)	0	4 (8)	0·2	0	0, 0·3 (0·1)
11.	0	4	0	1·2	0·1	20 (12)	0	0·8 (1·2)	0, 0
12.	0·2 (0·1)	0·05 (0·1)	16	0·2	0	0	0·1 (0·4)	0	0, 0
13.	0·2	0	0·2 (0·4)	14 (18)	0·05 * (0)	0·1	0·1 (0·2)	0·1 (0·2)	0, 0
14.	0	0·2 (0·4)	0	12 (8)	0·15 (0·2)	8	0	0	0·1, 0·4 (0·2)

* A trace of sodium was found afterwards in the magnesium chloride solution

The results are considered satisfactory. Those obtained with reference to paper chromatograms are not inferior to results obtained otherwise. It is interesting to note that a complete analysis, including the two tests for cæsium, required <0·3 ml. of solution. If test (*c*) for cæsium were omitted and, as suggested in the preceding paper, the detection and determination of calcium and magnesium on the same chromatogram as strontium were put on a sound basis, then the whole analysis could be done on <0·1 ml. As a matter of interest, in the above analyses, the paper strips under examination for strontium were at the same time examined for barium, calcium, and magnesium before tests (*a*), (*b*), and (*d*) had been done. All three were correctly reported present or absent, except calcium in experiments 8 and 12, and barium in experiments 6 and 12. Loss of barium was attributed to its inadvertent precipitation as barium sulphate.

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CHEMISTRY DEPARTMENT,
KING'S BUILDINGS, EDINBURGH.

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701. *The Synthesis of Sugars from Simpler Substances. Part II.* The Synthesis of* DL-*Ribose* in vitro *from* D-*Glyceraldehyde and Glycollic Aldehyde.*

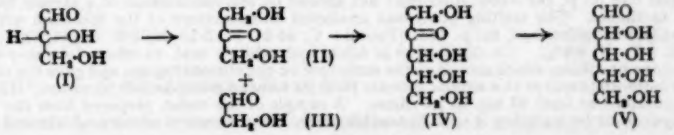
By. L. Hough and J. K. N. Jones.

Investigation of the pentose sugars produced from the reaction of D-glyceraldehyde with glycollic aldehyde, in the presence of lime-water, has resulted in the isolation of DL-ribose (as its toluene-*p*-sulphonylhydrazone) and of other DL-pentoses. The origin of the pentoses in Nature is discussed.

In Part I * it was observed that the products obtained from a solution of D-glyceraldehyde (I) and glycollic aldehyde (III) after 10 days at room temperature contained a complex mixture of pentose, hexose, and other sugars. A preliminary examination of this mixture on the paper chromatogram indicated that it contained all four pentose sugars (V), namely, arabinose, xylose, ribose, and lyxose. Conclusive evidence for the presence of DL-arabinose and DL-xylose was obtained by the separation of the mixture on a column of cellulose by partition chromatography and the formation, from the appropriate fractions, of crystalline DL-arabinose benzoylhydrazone and DL-xylose toluene-*p*-sulphonylhydrazone.

This reaction has now been repeated on a larger scale in the presence of lime-water, but allowed to proceed for one day only. The resultant mixture of sugars (*A*) was separated on a column of cellulose by partition chromatography at a temperature of 60° (Counsell, Hough, and Wadman, *Research*, 1951, **4**, 143). In this manner, an optically active fraction ($[\alpha]_D$ −10°), containing ribose as the only pentose sugar, was obtained. When this fraction was heated with toluene-*p*-sulphonhydrazide in methanol solution, crystalline DL-ribose toluene-*p*-sulphonylhydrazone was obtained. This derivative of D- and of DL-ribose is very sparingly soluble and is of value for both the characterisation and quantitative determination of ribose (*cf.* Easterby, Hough, and Jones, forthcoming publication). Two other fractions, possessing optical activity ($[\alpha]_D$ −10° and −12°, respectively) and containing pentose and other sugars, were also obtained.

The isolation of derivatives of the DL-pentose sugars, rather than of their optically active isomers, may be attributed to the predominant formation of the racemic sugars and also to the greater insolubility of their derivatives. Undoubtedly, some optically active sugars, some of which may be pentoses, are formed, but their identity is as yet unknown. The presence in the pentose fractions of such sugars as apiose and dendroketose, which because of their mode of synthesis will be optically inactive, and of optically active sugars such as hamamelose and psicose, is also to be expected (*cf.* Hough and Jones, *Nature*, 1951, **167**, 180). It would appear, therefore, that either the D-glyceraldehyde (I) concerned with pentose synthesis is first epimerised to



dihydroxyacetone (II), which may then react with the glycollic aldehyde (III) to yield DL-pentoses (V), or, alternatively, the D-glyceraldehyde is racemised to DL-glyceraldehyde before reaction with glycollic aldehyde. In this connection it is noteworthy that Fischer and Baer (*Helv. Chim. Acta*, 1936, **19**, 519) found that D-glyceraldehyde in alkaline solution is first converted into dihydroxyacetone, followed by reaction of the two to give D-ketohexoses. Dihydroxyacetone will, in fact, condense with glycollic aldehyde to give DL-pentose sugars (Hough and Jones, *loc. cit.*), and an examination of the condensation products (*A* : see above) from glycollic aldehyde and D-glyceraldehyde revealed that ketopentoses (IV) were present, since on the paper chromatogram they gave a characteristic blue colour with the resorcinol–hydrochloric acid spray reagent and moved at the same rate as riboketose and xyloketose. We consider, therefore, that in the above pentose synthesis, the main reaction involves the conversion of D-glyceraldehyde into dihydroxyacetone, which then reacts with glycollic aldehyde

* Part I, *J.*, 1951, 1122.

to give ketopentoses (IV), epimerisation of which affords the DL-pentose sugars. From this point of view, it is noteworthy that dihydroxyacetone phosphate will react with glycollic aldehyde in the presence of an aldolase of animal origin to give phosphorylated ketopentoses (Meyerhof and Kiessling, *Biochem. Z.*, 1935, **279**, 40; Lohmann and Schuster, *ibid.*, 1936, **286**, 301, 319; Schlenk and Waldvogel, *Fed. Proc.*, 1947, **6**, 288; Racher, *ibid.*, 1948, **7**, 180). The direct reaction of D-glyceraldehyde with glycollic aldehyde to give optically active pentose may also occur, but this reaction can occur in two different ways; by aldol-type condensation:

$$CH_2(OH)\cdot CH(OH)\cdot CHO + CH_2(OH)\cdot CHO \longrightarrow CH_2(OH)\cdot CH(OH)\cdot CH(OH)\cdot CH(OH)\cdot CHO$$

or by acyloin-type condensation:

$$CH_2(OH)\cdot CH(OH)\cdot CHO + OHC\cdot CH_2\cdot OH \longrightarrow CH_2(OH)\cdot CH(OH)\cdot CH(OH)\cdot CO\cdot CH_2\cdot OH.$$

Evidence for the latter type of reaction has been provided by Rappoport, Barker, and Hassid (*Arch. Biochem. Biophys.*, 1951, **31**, 326). Since Tewfik and Stumpf (*Amer. J. Bot.*, 1949, **36**, 567) have demonstrated the wide occurrence of aldolase in plants, it is conceivable that the pentoses are formed in Nature as their phosphorylated derivatives, *via* glycollic aldehyde and dihydroxyacetone derivatives (see Benson, *J. Amer. Chem. Soc.*, 1951, **73**, 2971), and that the reaction between derivatives of D-glyceraldehyde and glycollic aldehyde is of less common occurrence.

Experimental.

Reaction of D-*Glyceraldehyde with Glycollic Aldehyde.*—D-Glyceraldehyde (9·0 g.) (Baer and Fischer, *J. Biol. Chem.*, 1939, **128**, 463) was dissolved in water (75 c.c.) and glycollic aldehyde (6·0 g.) (prepared from 17 g. of dihydroxymaleic acid) in water (75 c.c.) was added. The solution was made alkaline by the addition of a slight excess of calcium hydroxide and the mixture set aside at 20° in a stoppered vessel. After 45 minutes a sample of the solution was examined on the paper chromatogram and observed to contain pentose sugars. After 20 hours the calcium was precipitated by addition of oxalic acid solution, and the solution after filtration de-ionised by passage through a column of Amberlite resin 1R4B. The aqueous solution was then concentrated, under reduced pressure, to a syrup (11·9 g.), which was fractionated by partition chromatography on a column of cellulose at 60°, butanol saturated with water at room temperature being used as the mobile phase (Counsell, Hough, and Wadman, *loc. cit.*). Concentration of the appropriate fractions of the effluent from the column (see Hough and Jones, *J.*, 1951, 1122, for details) gave five main fractions.

Fraction 1 (1·3 g.), consisted of glyceraldehyde, glycollic aldehyde, and ketopentoses. The ketopentoses move faster than ribose in the butanol–pyridine–water solvent (Hough and Jones, *loc. cit.*) and give a characteristic blue colour with the resorcinol–hydrochloric acid spray reagent. The positions of these sugars and their colour reactions were identical with those obtained from the ketopentose sugars obtained by epimerising arabinose and xylose, respectively. The glyceraldehyde and glycollic aldehyde moved faster than the ketopentose sugars and gave orange colours with the *p*-anisidine hydrochloride spray.

Fraction 2 (1·4 g.) ($[\alpha]_D$ −9°; *c*, 1·1 in water), contained ribose as the main component. The solution of sugars (1·3 g.) in methanol (25 c.c.) with toluene-*p*-sulphonhydrazide (1·8 g.) was boiled under reflux for 30 minutes. On cooling, DL-*ribose toluene*-p-*sulphonylhydrazone* (0·193 g.) crystallised. This material had m. p. 161—162° (decomp.) not altered on recrystallization of a sample from a large volume of methanol. The melting point was unaltered on admixture of the specimen with D-ribose toluene-*p*-sulphonylhydrazone, m. p. 164° (Found: C, 45·3; H, 5·7; N, 8·8. $C_{12}H_{18}O_4N_2S$ requires C, 45·3; H, 5·7; N, 8·8%). On dissolution in dilute hydrochloric acid, DL-ribose toluene-*p*-sulphonylhydrazone gave DL-ribose, which moved at the same rate on the chromatogram and gave the same colour reaction as D-ribose prepared in a similar manner from its toluene-*p*-sulphonylhydrazone. This fraction therefore contained at least 93 mg. of DL-ribose. A sample of the sugar, prepared from the toluene-*p*-sulphonylhydrazone by warming it with benzaldehyde in the presence of acetic acid, showed no optical activity.

Fraction 3 (1·8 g.) ($[\alpha]_D$ −10°; *c*, 0·11 in water), when examined on the paper chromatogram, showed ribose, xylose, and lyxose, together with other sugars and traces of arabinose. It was not further examined.

Fraction 4 (2·3 g.) ($[\alpha]_D$ −12°; *c*, 0·23 in water) contained arabinose, xylose, and other sugars. It was heated under reflux with benzhydrazide (2·1 g.) in methanol (25 c.c.) for 30 minutes. After the solution had cooled, DL-arabinose benzoylhydrazone (55 mg.), m. p. and mixed m. p. 195°, was collected.

Fractions 5 (1·7 g.) and 6 (1·7 g.) and the residue on the column did not contain pentose sugars and were not further examined.

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702. *The Cardiac Glycosides of* Urechites suberecta.

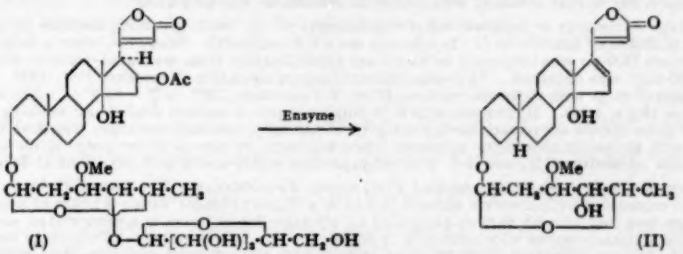
By C. H. Hassall.

Urechitoxin, $C_{38}H_{58}O_{14}$, isolated from leaves of *Urechites suberecta* in which enzymic hydrolysis is inhibited, is formulated as glucosido-oleandrin. When enzymic hydrolysis is permitted, deacetylanhydro-oleandrin and oleandrin are obtained.

The presence of toxic compounds in the shrub *Urechites suberecta* Muell. Arg. (family Apocynaceæ) has been recognised for some time. Dancer ("The Medical Assistant," 1801) records the use of the leaves as a poison. It is said to have been widely employed for this purpose in Obeah practices in Jamaica in the eighteenth and nineteenth centuries (Bowrey, *Proc. Roy. Soc.*, 1878, **27**, 309). Descourtilz ("Flore pittoresque et medicale des Antilles," 1829, Vol. VII, p. 68) described medicinal uses of the plant.

The first experiments on the isolation of active constituents were by Bowrey (*J.*, 1878, **33**, 252) who obtained two crystalline products, urechitoxin and urechitin. Minckiewiz (Dissertation, Dorpat, 1888), apparently without knowledge of Bowrey's work, also obtained two crystalline substances which were, however, incompletely characterised and had limited biological activity. The similarity of the toxic action of the constituents of the leaves to that of cardiac glycosides of the digitalis series has been confirmed by several investigators (Stockman, *Lab. Reports, Royal College of Physicians*, 1892, **4**, 64).

Although Bowrey did not obtain any direct evidence of the nature of urechitoxin and urechitin he made two observations which, when interpreted in terms of current knowledge of the cardiac glycoside series, suggested the possibility of a relation between gitoxin and these compounds. On hydrolysis of urechitoxin with concentrated hydrochloric acid a yellow, crystalline compound, termed urechitoxetin, was obtained. The properties of this product correspond to those of the yellow compound dianhydro-gitoxigenin, $C_{23}H_{30}O_3$, obtained on vigorous hydrolysis of oleandrin. When Bowrey heated urechitin at 200° a volatile acid was formed. This is reminiscent of Hesse's observation (*Ber.*, 1937, **70**, 2264) that oleandrin, when strongly heated, yields 16-deacetylanhydro-oleandrin and acetic acid.



The relationship of the glycosides to oleandrin has been established. When enzymic hydrolysis is permitted, a mixture of deacetylanhydro-oleandrin (II) and oleandrin can be isolated from an alcoholic extract of the leaves. When enzyme action is prevented by maceration of fresh leaves with absolute alcohol, urechitoxin is the principal product. Urechitoxin, $C_{38}H_{58}O_{14}$, $\lambda_{max.}$ 220 ($\log \varepsilon$ 4·24), contains one methoxyl group and gives no Keller–Kiliani reaction. It is hydrolysed by an enzyme preparation from the leaves to deacetylanhydro-oleandrin and glucose. This estalishes its identity as glucosido-oleandrin (I). Two similar glycosides, cryptograndoside B (Aebi and Reichstein, *Helv. Chim. Acta*, 1950, **33**, 1031) and hongheloside C (Hunger and Reichstein, *ibid.*, p. 76), have recently been isolated. In these compounds sarmentose and cymarose respectively replace the oleandrose present in urechitoxin (I).

Information has recently been made available through the courtesy of Professor T. Reichstein of a preliminary study (A. Hunger, to be published) on the glycosides present in the related species *Urechites lutea*. Several crystalline products were isolated and the identity of the principal constituent as deacetylanhydro-oleandrin was established.

Experimental.

Isolation of Cardiac Glycosides after Preliminary Fermentation.—In a typical experiment, the leaves of mature plants (6 kg.) collected in Jamaica were macerated in a Waring blender and set aside, just covered by water and a supernatant layer of toluene, for 7 days. The solid residue obtained on filtration was set aside for 2 days with absolute ethanol (9 l.). The solid was filtered off and washed with alcohol (2 × 1·5 l.). The filtrate and washings were stirred with moist lead hydroxide (prepared from 190 g. of lead acetate and washed until washings were neutral). The yellow lead complex was filtered off, washed with alcohol (2 × 500 c.c.), and discarded. The filtrate and washings were concentrated *in vacuo* at a temperature not exceeding 40°. As the light green filtrate became concentrated, a dark green, tarry product separated. This was free from glycoside. The alcoholic solution was separated from tar by decantation until a stage was reached when no significant amount of tar separated. Further concentration until the bulk of the alcohol was removed left a suspension of light green, semicrystalline product in aqueous solution. The solid (36 g.) was filtered off, dried, and extracted with light petroleum (b. p. 60—80°; 3 × 75 c.c.) to remove wax and with ethyl acetate to remove tar, pigment, and further wax. The crude product remaining was recrystallised (charcoal) from methanol–water. The crude glycoside obtained in this way was mixed with further purified material isolated from the mother-liquors. The colourless, crystalline product (26·3 g.; yield on fresh leaves, 0·47%), m. p. 210—240°, $[\alpha]_D^{20}$ +4·0° (*c*, 0·7 in chloroform), was subjected to paper chromatography using ethyl acetate–water (Hassall and Martin, *J.*, 1951, 2766). This indicated the presence of two products, of R_{FF} 0·96 and 0·87 respectively at 35°.*

16-*Deacetylanhydro-oleandrin.*—When the mixture of glycosides (0·89 g.) was subjected to fractional elution chromatography on neutral activated alumina (30 g.) with, successively, 1 : 3 chloroform–benzene (10 × 100-c.c. fractions), 1 : 1 chloroform–benzene (6 × 100 c.c.), and chloroform (5 × 100 c.c.), amorphous material (18 mg.) separated in the first fraction. Fractions 2—10 (0·425 g.) consisted of a mixture with ultra-violet absorption characteristics similar in type to the original product, while material from later fractions (m. p. 230°) was found to consist of essentially pure 16-deacetylanhydroglycoside. The latter fractions were recrystallised from methanol–water, to give plates, $[\alpha]_D^{20}$ +16·2° (*c*, 1·1 in methanol), $\lambda_{max.}$ 271 mμ. (log ε 4·21) (Found: C, 69·55; H, 8·6; OMe, 5·4. Calc. for $C_{36}H_{44}O_7$: C, 69·7; H, 8·6; OMe, 6·0%). Legal, Raymond (*Analyst*, 1939, **64**, 113), and Keller–Kiliani reactions were positive. The m. p. and mixed m. p. with authentic 16-deacetylanhydro-oleandrin (kindly provided by Professor T. Reichstein) was 232—234°.

The acetate, needles from acetone–ether, had m. p. and mixed m. p. with authentic material 209—211°. Hydrolysis of the glycoside (50 mg.) in methanol (5 c.c.) and 0·1N-sulphuric acid (2 c.c.) gave, on working up in the usual way, aglycone corresponding to 16-anhydrogitoxigenin (Aebi and Reichstein, *Helv. Chim. Acta*, 1950, **33**, 1028; Hesse, *Ber.*, 1937, **70**, 2264), m. p. 244—245°, $[\alpha]_D^{20}$ +95·5 (*c*, 1·52 in methanol) (Found: C, 73·95; H, 9·0. Calc. for $C_{23}H_{32}O_4$: C, 74·2; H, 8·7%), and a sugar which on paper chromatography in which 3 : 3 : 1 ethyl acetate–water–acetic acid was used (Jermyn and Isherwood, *Biochem. J.*, 1949, **44**, 402) with aniline hydrogen phthalate as indicator (Partridge, *Nature*, 1949, **164**, 443), gave a spot corresponding to that obtained with authentic oleandrose, R_{FC} 0·53 at 35°.

Oleandrin.—Attempts to separate other constituents of the crude glycoside mixture by chromatography on alumina or talc–Celite (1 : 2) columns were not successful. However, when a large quantity of the mixture (3·0 g.) was subjected to fractional crystallisation from methanol–water a more soluble fraction (80 mg.) was obtained. This was characterised as oleandrin (Neumann, *Ber.*, 1937, **70**, 1547), m. p. and mixed m. p. with authentic material (Prof. T. Reichstein) 250°, $[\alpha]_D^{25}$ −48·0° (*c*, 1·3 in methanol), $\lambda_{max.}$ 220 mμ. (log ε, 4·20). Hydrolysis with 0·1N-sulphuric acid in methyl alcohol and working up in the usual way gave results on paper chromatography of the aglycone and the sugar identical with those obtained with authentic oleandrin : aglycone (oleandrigenin), by use of water–butyl alcohol, R_{FF} 0·62 at 34°; sugar (oleandrose), by use of 3 : 3 : 1 ethyl acetate–water–acetic acid, R_{FC}, 0·55 at 34°.

Isolation of Cardiac Glycosides without Preliminary Fermentation.—The leaves (2 kg.) of mature plants were macerated with absolute ethanol (1·5 l.) in a Waring blender within 2 hours of being picked. The mixture was treated with further alcohol (2 l.), set aside for 24 hours in a refrigerator, and filtered, and the solid material washed with alcohol (2 × 500 c.c.). The mixed extract and washings were treated with lead hydroxide (prepared from 90 g. of acetate and washed until washings were neutral) then evaporated *in vacuo* at < 40° until all the alcohol was removed. The aqueous solution was decanted from a resinous product that separated and was extracted with light petroleum (b. p. 60—80°; 3 × 100 c.c.) to remove green pigment, and then with chloroform (2 × 100 c.c.). The aqueous solution, which no longer gave a positive Legal reaction and was not bitter, was discarded. This chloroform extract was mixed with a chloroform extract of the resinous product, which contained the cardiac glycoside present in this fraction, dried (Na_2SO_4), and evaporated. The amorphous residue (10·0 g.) was extracted with light petroleum (b. p. 60—80°; 5 × 100 c.c.) which removed a small amount of pigment and wax. The remaining resin was recrystallised from 30% methanol–water, to give a crude, crystalline product, m. p. 150° (4·3 g.). A further small yield (0·21 g.) of similar material was isolated from the mother-liquors on concentration. No further crystalline material could be separated by repeated recrystallisation of the amorphous product.

Urechitoxin.—The crude, crystalline product was employed for paper chromatography, ethyl acetate–water and water–butanol mixtures being used. Single spots R_{FF} 0·82 and 0·00 respectively at 35° were obtained in each case. Fractional elution chromatography, with Celite–talc (2 : 1) and increasing concentrations of chloroform in benzene gave no indication of a second component. The product was

* The ultra-violet absorption spectra, $\lambda_{max.}$ 220 mμ (log ε 4·10) and 262 mμ (log ε 3·85) suggested a mixture containing a 16-deacetylanhydroglycoside and a glycoside with no unsaturation at $C_{(16)}$.

recrystallised from 30% methanol as stout prisms, m. p. 157—159° (Found: C, 62·2; H, 8·2; OMe, 4·6. $C_{28}H_{44}O_{14}$ requires C, 61·8; H, 7·9; 1OMe, 4·2%). The Legal and Raymond reaction were positive (red; blue), the Keller–Kiliani reaction negative. $\lambda_{max.}$ was 220 mμ. (log ε, 4·24), and $[\alpha]_D^{27}$ −58·4° (*c*, 0·87 in methanol); the colour with 85% sulphuric acid was yellow (immediate), carmine red (1 minute), grey (60 minutes). The acetyl derivative was amorphous.

Enzymatic Hydrolysis of Urechitoxin.—An enzyme preparation was obtained by macerating the fresh leaves (200 g.) of *Urechites suberecta* with water in a Waring blender, and precipitating the crude enzyme with ethanol (1 l.). The precipitate was dissolved in water (100 c.c.), reprecipitated with ethanol (500 c.c.), filtered off, and dried (weight, 1·4 g.). The crude enzyme (100 mg.), urechitoxin (100 mg.), and water (5 c.c.) were set aside at room temperature for 7 days with a supernatant layer of toluene. The suspension was filtered, washed with water, dried, and extracted with methanol. The aqueous solution was concentrated and examined for sugar constituents by paper chromatography. The methanolic solution was evaporated to yield a white, crystalline solid, m. p. 210°, which, recrystallised from 40% ethanol, had m. p. and mixed m. p. with authentic 16-deacetylanhydro-oleandrin 232—234°. The crude product, $\lambda_{max.}$ 220 (log ε, 3·7) and 270 mμ. (log ε, 4·1), appeared still to contain a small proportion of a 16-acetyl-glycoside (cf. Aebi and Reichstein, *Helv. Chim. Acta*, 1950, **33**, 1013).

Paper chromatography of the aqueous solution at 35° with ethyl acetate–water–acetic acid (3 : 3 : 1) for 30 hours according to Jermyn and Isherwood (*loc. cit.*) and Partridge (*loc. cit.*) gave a single spot (with centre 5·0 cm. from starting line). Mannose, glucose, and fructose, used for comparison in the same experiment, gave spots 6·0, 5·0, and 7·6 cm. distant respectively. This indicates the identity of the unknown hexose sugar with glucose (Hirst and Jones, "Chromatographic Analysis," *Faraday Soc. Disc.*, 1949, **7**, 268).

Acid Hydrolysis of Urechitoxin.—Urechitoxin (180 mg.) in methanol (5 c.c.) was refluxed for 25 minutes with 0·1N-sulphuric acid (5 c.c.). The methyl alcohol was evaporated *in vacuo* and the aglycone separated by filtration. The aqueous solution was extracted with chloroform (6 × 200 c.c.), neutralised with barium carbonate, filtered, and evaporated *in vacuo* at room temperature. The recrystallised aglycone (from methanol–ether), m. p. 241—243°, $[\alpha]_D^{26}$ −6·2° (*c*, 0·91), R_{BB} (water–*n*-butyl alcohol) 0·52 at 35°, was identified as oleandrigenin by direct comparison with an authentic sample.

The water-soluble residue was subjected to paper chromatography for the sugar constituents. In a typical experiment (22 hours; 35°) the mixture gave three spots at distances 22·6, 2·8, and 0·8 cm., respectively, from the starting point. In the same experiment glucose and oleandrose gave spots 0·8 and 22·6 cm., respectively, from the starting point. When hydrolysis of urechitoxin was carried out for a longer period (1½ hours), the centre spot, which was the most intense in the first experiment, became less concentrated while the two spots corresponding to glucose and oleandrose increased in intensity. This suggests that the centre spot corresponds to glucosido-oleandrose. No further evidence was obtained on this point.

I am indebted to Mr. C. Brown for technical assistance, to Professor T. Reichstein for samples of authentic glycosides, and to Messrs. Roche Products Ltd. and the Chemical Society for grants. The analyses are by Dr. K. Ritter and Drs. G. Weiler and F. B. Strauss.

CHEMISTRY DEPARTMENT, UNIVERSITY COLLEGE OF THE WEST INDIES,
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703. *Terpene Compounds. Part VII.* The Synthesis and Reactions of 5-Keto-2-isopropylhexanoic † (γ-Acetyl-α-isopropylbutyric) Acid.*

By J. C. BARDHAN, N. C. DE, and (in part) B. B. DATTA.

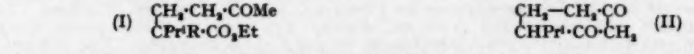
The synthesis of 5-keto-2-*iso*propylhexanoic acid,† based on a method described earlier (Bardhan, *J.*, 1940, 848), is reported. Sodium ethoxide converts the corresponding ethyl ester into the cyclic dione (II), which on treatment with phosphorus trichloride and ethyl sodiocyanoacetate, followed by hydrolysis, affords (±)-piperitone. The unsaturated cyano-ester (X) resulting from the action of ethyl 5-keto-2-*iso*propylhexanoate with ethyl cyanoacetate furnishes, on catalytic hydrogenation and hydrolysis, a crystalline modification, m. p. 87—88°, of β-methyl-α′-*iso*propylpimelic acid. This on ketonisation gives mainly (±)-*iso*menthone. The ester (X) and potassium cyanide give β-carboxy-β-methyl-α′-*iso*propylpimelic acid, m. p. 135—136°.

In connexion with our studies in the terpene series we required appreciable quantities of 5-keto-2-*iso*propylhexanoic * (γ-acetyl-α-*iso*propylbutyric) acid (cf. I; R = H). This acid has been obtained previously (Schimmel and Co., Report, 1910, Oct., p. 97; Simonsen, *J.*, 1921, **119**, 1653) by oxidation of piperitone with alkaline potassium permanganate. Obviously, this

* Part VI, *J.*, 1949, 197. † Geneva nomenclature (CO_2H = 1) is used throughout.

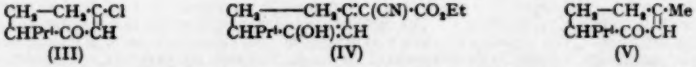
method is not suitable for the preparation of even moderately large quantities and the present communication reports a more convenient route, and also some reactions of this acid.

Following earlier work (Bardhan, *J.*, 1940, 848) we treated ethyl sodio*iso*propylmalonate with 4-diethylaminobutan-2-one methiodide, obtaining diethyl 6-keto-2-methylheptane-3 : 3-dicarboxylate (I; R = CO_2Et) in excellent yield. On alkaline hydrolysis followed by decarboxylation, this yielded 5-keto-2-*iso*propylhexanoic acid as a colourless liquid which readily formed a semicarbazone, m. p. 157°. The derived ethyl ester, on treatment with



(I) (II)

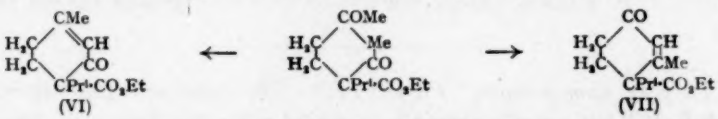
alcoholic sodium ethoxide, afforded the cyclic dione (II), m. p. 106—107°. When allowed to react with phosphorus trichloride according to the general method of Crossley and Le Sueur (*J.*, 1903, **83**, 117; 1902, **81**, 675, 821) (II) gave the corresponding unsaturated chloro-ketone (III) as an apprently homogeneous liquid, which was hydrogenated over palladium to 2-*iso*propyl*cyclo*hexanone, identified by comparison with an authentic specimen (Kötz and Michels, *Annalen*, 1906, **350**, 204). The structure of (III) is, moreover, in accord with the behaviour of dihydro-1 : 1 : 2-trimethylresorcinol towards phosphorus trichloride (Crossley and Renouf, *J.*, 1911, **99**, 1102).



(III) (IV) (V)

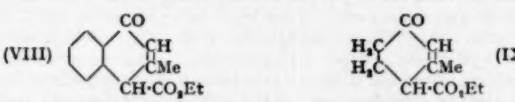
3-Chloro-6-*iso*propyl*cyclo*hex-2-enone (III) and ethyl sodiocyanoacetate readily afford a crystalline acidic product, to which the enolic structure (IV) is assigned by analogy with other substances of this class (cf. Crossley and Gilling, *J.*, 1910, **97**, 526). On being heated with an excess of concentrated hydrochloric acid the unsaturated cyano-ester (IV) decomposes almost quantitatively, giving an unsaturated ketone (V) the physical constants of which, as well as of several derivatives, closely corresponded with those of (±)-piperitone and its derivatives (Read and Smith, *J.*, 1922, 1871; Simonsen, *loc. cit.*). Incidentally, the formation of piperitone as the sole product of the above series of reactions provides further proof of the correctness of the structure of (III).

Walker (*J.*, 1935, 1585) has effected a simple synthesis of (±)-piperitone by condensing 2-chloroethyl methyl ketone with ethyl sodio*iso*propylacetoacetate and has interpreted the reaction as proceeding through the intermediate (VI). The formation of an isomeric product



(VI) (VII)

(VII) can however not be precluded, especially since in all such reactions the latter type of product is more frequently encountered. Thus, according to Barrett, Cook, and Linstead (*J.*, 1935, 1067) ethyl sodioacetoacetate and acetyl*cyclo*hexene give the keto-ester (VIII), and Mannich and Fourneau (*Ber.*, 1938, **71**, 2090) have prepared (IX) by the action of sodium



(VIII) (IX)

ethoxide on a mixture of ethyl acetoacetate and 4-diethylaminobutan-2-one. However, we find that ethyl sodio*iso*propylacetoacetate and diethylaminobutanone methiodide readily yield a product hydrolysed to (±)-piperitone (V), with no trace of the isomeric ketone corresponding to (VII); this unexpected behaviour is probably due to the presence of the substituent which greatly reduces the tendency of the adjacent carbonyl group to participate in ring formation in the usual way. Further work will be necessary to clear up this point.

Ethyl 5-keto-2-*iso*propylhexanoate (I; R = H) readily condensed with ethyl cyanoacetate in presence of ammonium acetate–acetic acid (cf. Cope and his co-workers, *J. Amer. Chem. Soc.*, 1941, **63**, 3452), to give diethyl 1-cyano-2 : 6-dimethylhept-1-ene-1 : 5-dicarboxylate (X). This on hydrogenation in alcohol over Adams's platinum oxide furnished the saturated ester

(XI) and, on hydrolysis with an excess of concentrated hydrochloric acid, (XI) yielded β-methyl-α′-*iso*propylpimelic acid, m. p. 87—88° (hitherto reported as an oil; Kötz and Schwarz, *Annalen*, 1907, **357**, 209; Kötz and Hesse, *ibid.*, 1905, **342**, 306). The acid on distillation in

$CO_2Et{\cdot}CHPr^i{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{:}C(CN){\cdot}CO_2Et$ (X) $\qquad$ $CO_2Et{\cdot}CHPr^i{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH(CN){\cdot}CO_2Et$ (XI)

presence of small amounts of barium hydroxide at 310—330° afforded mainly (±)-*iso*menthone (semicarbazone, m. p. 222—223°) (cf. Hughesdon, Smith, and Read, *J.*, 1923, **123**, 2922).

The unsaturated cyano-ester (X) and alcoholic potassium cyanide (Lapworth and McRea, *J.*, 1922, **121**, 2752) gave a product which on hydrolysis and elimination of carbon dioxide

$$CO_2H{\cdot}CHPr^i{\cdot}CH_2{\cdot}CH_2{\cdot}CMe(CO_2H){\cdot}CH_2{\cdot}CO_2H \quad \text{(XII)}$$

yielded 2 : 6-dimethylheptane-1 : 2 : 5-tricarboxylic acid (XII), m. p. 135—136°. We hope to deal with the reactions of (XII) in a later communication.

Experimental.

Diethyl 6-*Keto*-2-*methylheptane*-3 : 3-*dicarboxylate* (I; R = CO_2Et).—Ethyl *iso*propylmalonate (60·6 g.) was added to a solution of sodium (6·9 g.) in absolute alcohol (120 ml.) and, to the mixture, cooled in ice, 4-diethylaminobutan-2-one methiodide (from 43 g. of ketone, prepared according to Wilds and Shunk, *J. Amer. Chem. Soc.*, 1943, **65**, 472, and 22·5 ml. of methyl iodide), dissolved in a little absolute alcohol, was gradually introduced. After 5 hours at 0°, the mixture was kept at room temperature overnight and then refluxed on the steam-bath for 4 hours. On cooling it was diluted with water, slightly acidified with dilute hydrochloric acid, and repeatedly extracted with benzene. The benzene layer was washed, dried, and evaporated, and the residue distilled under diminished pressure. *Diethyl* 6-*keto*-2-*methylheptane*-3 : 3-*dicarboxylate* (53·6 g.) formed an almost colourless oil having a characteristic odour and b. p. 140°/4 mm. (Found: C, 61·7; H, 8·8. $C_{14}H_{24}O_5$ requires C, 61·8; H, 8·8%). The *semicarbazone*, on recrystallisation from dilute alcohol formed minute prisms, m. p. 146° (Found: C, 54·8; H, 8·3. $C_{15}H_{27}O_5N_3$ requires C, 54·7; H, 8·3%).

5-*Keto*-2-iso*propylhexanoic Acid* (*as* I; R = H).—The foregoing ester (82·5 g.) was boiled under reflux with potassium hydroxide (44 g.) in water (36 ml.) and alcohol (186 ml.) for 1 hour, the alcohol was removed as completely as possible, the residue diluted with water and extracted with ether, and the extract discarded. The alkaline solution was acidified with dilute hydrochloric acid and again extracted with ether. After removal of the ether the residue was heated in an oil-bath at 130—140° until evolution of carbon dioxide ceased (2—3 hours). 5-*Keto*-2-iso*propylhexanoic acid* was obtained as a colourless somewhat viscous liquid, b. p. 139—140°/5 mm. (Found: C, 62·7; H, 9·4. $C_9H_{16}O_3$ requires C, 62·8; H, 9·3%). The *semicarbazone* (from alcohol) had m. p. 157° (Found: C, 52·6; H, 8·3. $C_{10}H_{19}O_3N_3$ requires C, 52·4; H, 8·3%). The *ethyl* ester, prepared by refluxing the acid with an excess of 3% alcoholic hydrogen chloride for 6 hours, formed a colourless oil, having a characteristic sweet smell and b. p. 103—104°/3 mm. (Found: C, 65·9; H, 9·9. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·0%). The *semicarbazone*, separate sfrom aqueous alcohol in shining plates, m. p. 124° (Found: C, 55·9; H, 8·9. $C_{12}H_{23}O_3N_3$ requires C, 56·0; H, 9·0%).

4-iso*Propyl*cyclo*hexane*-1 : 3-*dione* (II).—The foregoing hexanoate (22 g.), mixed with a solution of sodium (2·8 g.) in absolute alcohol (90 ml.), was refluxed on the steam-bath for 20 hours. On cooling it was diluted with water, excess of alcohol was removed on the steam-bath as completely as possible, and the clear alkaline solution was washed with ether, separated, and acidified with dilute sulphuric acid. The product which at first separated as an oil quickly solidified. This was collected, washed with water, and dried. The *diketone* crystallises from benzene–light petroleum (b. p. 60—80°) in colourless, compact prisms (17 g.), m. p. 106—107° (Found: C, 69·9; H, 9·3. $C_9H_{14}O_2$ requires C, 70·1; H, 9·1%). It has acidic character, and its solution in alcohol gives a pink colour with ferric chloride.

3-*Chloro*-6-iso*propyl*cyclo*hex*-2-*enone* (III).—A mixture of the diketone (II) (22·5 g.), dry chloroform (45 ml.), and phosphorus trichloride (4·5 ml.) was heated under reflux for 3 hours. The chloroform was distilled off, and the viscous residue treated with water and extracted with ether. The ethereal solution was washed with 4% sodium hydroxide solution, then with water, dried, and evaporated. 3-*Chloro*-6-iso*propyl*cyclo*hex*-2-*enone* distilled constantly as a colourless, highly refractive oil (14 g.), b. p. 93°/4 mm. (Found: Cl, 20·8. $C_9H_{13}OCl$ requires Cl, 20·6%).

The chloro-ketone (5 g.) was shaken in alcohol (30 ml.) in an atmosphere of hydrogen in the presence of gum arabic (0·1 g.), dissolved in a little water, and palladium chloride (0·1 g.) until the calculated amount of hydrogen (2 mols.) was absorbed (cf. France, Heilbron, and Hey, *J.*, 1939, 1290). The solution was filtered, and treated with an excess of semicarbazide acetate solution. After being kept overnight the crystalline precipitate, purified from dilute alcohol, m. p. 187—188° (Found: C, 60·6; H, 9·7. Calc. for $C_{10}H_{19}ON_3$: C, 60·9; H, 9·6%), showed no depression when mixed with the semicarbazone (m. p. 187°) of 2-*iso*propyl*cyclo*hexanone (Kötz and Michels, *loc. cit.*). The regenerated ketone had b. p. 63—65°/4 mm. and proved to be 2-*iso*propyl*cyclo*hexanone (Found: C, 77·1; H, 11·5. Calc. for $C_9H_{16}O$: C, 77·1; H, 11·4%).

Ethyl α-*Cyano*-α-(3-*hydroxy*-4-iso*propyl*cyclo*hex*-2-*enylidene*)*acetate* (IV).—To a solution of sodium (2·5 g.) in alcohol (dried over calcium) (34 ml.) ethyl cyanoacetate (12·4 ml.) was added, the solution cooled, and chloro*iso*propyl*cyclo*hexenone (III) (9·4 g.) gradually added, care being taken to avoid rise of temperature. Next morning the reaction mixture was heated on the water-bath for 6 hours, poured

into water, and extracted with ether. The aqueous alkaline liquid was then acidified with dilute sulphuric acid and repeatedly extracted with ether, and the ethereal solution washed, dried, and evaporated. The solid residual *ester*, on recrystallisation from chloroform–light petroleum (b. p. 60—80°), formed minute colourless prisms, m. p. 124° (10 g.) (Found: C, 67·3; H, 7·5. $C_{14}H_{19}O_2N$ requires C, 67·5; H, 7·7%). It is moderately soluble in most organic solvents and almost insoluble in light petroleum. It dissolves in sodium carbonate solution with effervescence and gives with ferric chloride in alcoholic solution a fine emerald-green colour.

(±)-*Piperitone* (V).—The cyano-ester (IV) (12 g.) was refluxed (sand-bath) with concentrated hydrochloric acid (120 ml.) for 6 hours. The solid gradually disappeared with evolution of carbon dioxide, and an oil separated. On cooling the liquid was diluted with water and extracted with ether, the ethereal solution washed, dried, and evaporated, and the residue distilled under diminished pressure; nearly the whole boiled at 104—106°/8 mm. The yield was 5·5 g. The semicarbazone is best prepared by boiling the ketone with aqueous-alcoholic semicarbazide acetate for 6 hours. The insoluble product which separated, on recrystallisation from acetic acid, formed minute leaflets, m. p. 226—227° (Found: C, 63·1; H, 9·1. Calc. for $C_{11}H_{19}ON_3$: C, 63·2; H, 9·1%). The mother-liquor yielded a small quantity of a more soluble semicarbazone, which on repeated crystallisation from alcohol (charcoal) afforded microscopic needles, m. p. 174—175° (Found: C, 63·3; H, 9·0. Calc. for $C_{11}H_{19}ON_3$: C, 63·2; H, 9·1%). There can be little doubt that these are identical with the α- (m. p. 226—227°) and the β-semicarbazone (m. p. 174—176°) respectively of (±)-piperitone (cf. Read and Smith, *loc. cit.*, p. 1868; Simonsen, *loc. cit.*). The ketone regenerated from the semicarbazone (m. p. 226—227°) on distillation in a vacuum formed a colourless transparent oil having b. p. 78°/4 mm., $d_4^{24\cdot5}$ 0·9295, $n_D^{24\cdot5}$ 1·4822, $[R_L]_D$ 46·63 (Calc., 45·72) (Found: C, 78·9; H, 10·5. Calc. for $C_{10}H_{16}O$: C, 78·9; H, 10·5%). Read and Smith (*loc. cit.*) give b. p. 113°/18 mm.; d_4^{20} 0·9331, n_D^{20} 1·4845, $[R_L]_D$ 46·70. The substance has a pronounced odour reminiscent of peppermint. The piperonylidene derivative, prepared according to Earl and Read (*J.*, 1926, 2075), had m. p. 128° (Found: C, 75·9; H, 7·1. Calc. for $C_{18}H_{20}O_3$: C, 76·0; H, 7·1%).

Action of Ethyl Sodioisopropylacetoacetate on 4-Diethylaminobutan-2-one Methiodide.—A solution of ethyl *iso*propylacetoacetate (34·4 g.) in alcoholic sodium ethoxide (4·6 g. of sodium in 80 ml. of alcohol) was cooled in ice, and diethylaminobutanone methiodide (Mannich base, 28·1 g.; methyl iodide, 14·2 ml.) in alcohol (20 ml.) gradually added. After being kept overnight the solution was refluxed for 4 hours, cooled, diluted with water, acidified with hydrochloric acid, and extracted with ether. After removal of the solvent from the dried ethereal layer the residue on distillation afforded 32 g. of a liquid, b. p. 95—160°/12 mm. This was refluxed with acetic acid (100 ml.) and concentrated hydrochloric acid (50 ml.) for 30 hours. On cooling, the solution was diluted with water, saturated with ammonium sulphate, and extracted with ether. The ethereal solution was washed, dried, and distilled, giving (i) a colourless liquid having a characteristic ketonic odour (12·5 g.) and b. p. 104—105°/8 mm., and (ii) a somewhat viscous liquid (4 g.), b. p. 110—140°/8 mm. Fraction (i) on further purification through the semicarbazone (m. p. 226—227°) had b. p. 77—78°/3 mm., d_4^{24} 0·9290, n_D^{24} 1·4822, $[R_L]_D$ 46·66 (Found: C, 78·7; H, 10·4. Calc. for $C_{10}H_{16}O$: C, 78·9; H, 10·5%). The piperonylidene derivative, by which (±)-piperitone can be most readily characterised, had m. p. 127—128° as stated by Earl and Read (*loc. cit.*). Fraction (ii) above was not further examined.

Ethyl 1-*Cyano*-2 : 6-*dimethylhept*-1-*ene*-1 : 5-*dicarboxylate* (X).—Following Cope and his co-workers (*loc. cit.*), ethyl 5-keto-2-*iso*propylhexanoate (20 g.), ethyl cyanoacetate (11·3 ml.), ammonium acetate (3·8 g.), acetic acid (12 ml.), and benzene (50 ml.) were refluxed (oil-bath) at 150—160° for 4 hours. On cooling, the benzene layer was separated, washed with water, dried, and distilled. The unsaturated *ester* formed an almost colourless oil (23 g.), b. p. 175°/5 mm. (Found: C, 64·8; H, 8·5. $C_{14}H_{21}O_4N$ requires C, 65·0; H, 8·5%).

Ethyl 1-*Cyano*-2 : 6-*dimethylheptane*-1 : 5-*dicarboxylate* (XI).—The unsaturated ester (X) (31 g.) was shaken in alcohol (30 ml.) at the room temperature with palladised charcoal (*Org. Synth.*, **26**, 32) (1 g.) in an atmosphere of hydrogen until the required amount (2680 ml.) had been absorbed. The solution was filtered, excess of alcohol was distilled off at the water-pump, and the residue fractionated at diminished pressure to give the saturated *ester* (XI) as a colourless oil (30·5 g.), b. p. 168—170°/3 mm. (Found: C, 64·7; H, 9·3. $C_{14}H_{23}O_4N$ requires C, 64·6; H, 9·2%).

β-*Methyl*-α′-*iso*propylpimelic (2 : 6-*Dimethylheptane*-1 : 5-*dicarboxylic*) *Acid*.—The ester (XI) (29 g.) was heated with potassium hydroxide (16·8 g.), water (10 ml.), and alcohol (45 ml.) under reflux for 1 hour. The acidic material (24 g.), isolated in the usual way, was boiled for 10 hours with a mixture of sulphuric acid (40 ml.), acetic acid (53 ml.), and water (53 ml.), and, on cooling, the product was collected in ether. On evaporation of the solvent a dark brown oil remained which on storage in an evacuated desiccator over sulphuric acid gradually solidified to a crystalline mass (18 g.). This was esterified by heating it with alcohol (65 ml.) and sulphuric acid (5 ml.) for 6 hours. Ethyl β-methyl-α′-*iso*propylpimelate was obtained as a colourless liquid (17 g.), b. p. 128—129°/4 mm. (Found: C, 66·3; H, 10·4. Calc. for $C_{15}H_{28}O_4$: C, 66·2; H, 10·3%). Kötz and Schwarz (*loc. cit.*) give b. p. 151—152°/9 mm. This on hydrolysis with a 10% solution of alcoholic potassium hydroxide gave the acid as an oil which when rubbed with light petroleum (b. p. 60—80°) quickly solidified, and on repeated crystallisation from the same solvent formed aggregates of prisms, m. p. 87—88° (Found: C, 61·1; H, 9·2. Calc. for $C_{11}H_{20}O_4$: C, 61·1; H, 9·4%). The acid (2 g.) when heated with barium hydroxide (0·2 g.) at 310—330° (air-bath) yielded an oily distillate, which readily formed a semicarbazone, m. p. 222—223° (from alcohol) (Found: C, 62·3; H, 9·8. Calc. for $C_{11}H_{21}ON_3$: C, 62·56; H, 10·05%). The mother-liquor on evaporation afforded small quantity of an impure semicarbazone, which was not further examined. The ketone probably consists chiefly of (±)-*iso*menthone (Hughesdon, Smith, and Read, *loc. cit.*, give m. p. 225° and state that the m. p. is dependent on the rate of heating).

2 : 6-*Dimethylheptane*-1 : 2 : 5-*tricarboxylic Acid* (XII).—The unsaturated ester (X) (29·6 g.), dissolved in alcohol (125 ml.), was mixed with a solution of 98% potassium cyanide (11 g.) in water (25 ml.). The

solution, which became warm, was kept at the ordinary temperature for 4 days, then evaporated on the water-bath almost to dryness, concentrated hydrochloric acid (250 ml.) was added, and the whole heated under reflux (sand-bath) for 30 hours. The crude acid (25 g.) recovered from the ethereal extract was heated with absolute alcohol (50 ml.) and concentrated sulphuric acid (5 ml.) at 110—115° in a current of alcohol vapour for 6 hours. *Triethyl* 2 : 6-*dimethylheptane*-1 : 2 : 5-*tricarboxylate* thus obtained distilled constantly at 176°/4 mm. as a colourless mobile oil (Found: C, 62·9; H, 9·3. $C_{16}H_{28}O_6$ requires C, 62·8; H, 9·3%). Hydrolysis with alcoholic potassium hydroxide [4 g. in water (4 ml.) and alcohol (30 ml.)] for 1 hour yielded the corresponding *acid* as an oil which when rubbed with a little concentrated hydrochloric acid readily solidified. It crystallised from concentrated hydrochloric acid, in which it is sparingly soluble, in short prisms, m. p. 135—136° [Found: C, 55·3; H, 7·7%; equiv. (by titration), 87·0. $C_9H_{17}(CO_2H)_3$ requires C, 55·4; H, 7·7%; equiv., 86·7].

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UNIVERSITY COLLEGE OF SCIENCE AND TECHNOLOGY,
CALCUTTA.

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704. *Polynuclear Heterocyclic Systems. Part I. Introduction.*

By G. M. BADGER, R. S. PEARCE, and R. PETTIT.

The absorption spectra of several polynuclear heterocyclic aromatic compounds have been compared and contrasted with those of their carbocyclic analogues. Marked resemblances are noted, and the chief differences seem to be: (i) that the group-III absorption bands of the azahydrocarbons are much more intense than those of the hydrocarbons; (ii) that in the heterocyclic anthracene analogues (which do not exhibit group-III absorption) the group-II bands are sometimes slightly more intense than those of anthracene; (iii) that there is loss of fine structure in replacing a CH group by N; and (iv) that the absorption of the azahydrocarbons often begins at slightly longer wave-lengths than that of their hydrocarbon analogues.

IN many ways the aromatic heterocyclic systems closely resemble their carbocyclic analogues. Each annular nitrogen atom and each annular carbon atom contribute one π electron to the "aromatic sextet," so that pyridine, pyrimidine, and other nitrogen-containing aromatic compounds (termed aromatic azahydrocarbons) are all closely related to benzene and to substituted benzenes. Although the polynuclear heterocyclic systems have not yet been extensively investigated, it is known that many of the similarities are also to be found among the larger molecules. On the other hand, there are many important differences. For example, many of the aromatic azahydrocarbons undergo nucleophilic (anionoid) substitution very much more readily than the related hydrocarbons; many amino- and hydroxy-derivatives of aza-compounds are tautomeric and exist largely in quinonoid forms; some of the azahydrocarbons form highly coloured molecular compounds with their dihydro-derivatives; and so on. It seemed, therefore, that a systematic investigation of the relation between the aromatic hydrocarbons and their heterocyclic analogues, with particular reference to the polynuclear systems, would be of interest. In the present paper the ultra-violet absorption spectra of the aromatic nitrogen-containing compounds are compared and contrasted with those of the related aromatic hydrocarbons. This seemed necessary to enable the absorption spectra of the azahydrocarbons to be used for structural identification.

The aromatic hydrocarbons generally exhibit three main regions of absorption in the ultra-violet or the visible region. Benzene has an intense region of absorption (maximum at 1790 Å) in the far ultra-violet (Price and Walsh, *Proc. Roy. Soc.*, 1947, *A*, **191**, 22), a second region of relatively high intensity around 2000 Å, and a third region, of low intensity, around 2300—2600 Å (Henri, *J. Phys. Radium*, 1922, **3**, 180). Most of the dicyclic and polycyclic aromatic hydrocarbons also exhibit three main regions of absorption, the bands in each group being referred to as the group-I, -II, and -III bands, respectively, III being the region of low intensity (Braude, *Ann. Reports*, 1945, **42**, 123; Clar, "Aromatische Kohlenwasserstoffe," Berlin, 1941; Badger and Pearce, *J.*, 1950, 3072). The only exceptions are the linear condensed ring compounds anthracene, naphthacene, pentacene, etc., which show only two regions of absorption.

An examination of the published absorption curves of aromatic azahydrocarbons and of those now reported for the first time shows that these compounds also give rise to three main regions of absorption and that the two sets of curves have many features in common. Pyridine

has an intense region of absorption (maximum at 1700 Å) in the far ultra-violet (Price and Walsh, *loc. cit.*), a second region at about 2000 Å, and a third around 2500 Å (Menczel, *Z. physikal. Chem.*, 1927, **125**, 161; Swain, Eisner, Woodward, and Brice, *J. Amer. Chem. Soc.*, 1949, **71**, 1341). It is noteworthy, however, that although some of the maxima seem to be shifted towards shorter wave-lengths compared with benzene, the absorption of pyridine begins at somewhat longer wave-lengths, at about 2900 Å as against 2750 Å. Moreover, the intensity of absorption in the group-III region is about ten times as great for pyridine as for benzene. Similar comparisons can be made for other compounds. Maccoll (*J.*, 1946, 670) compared the group-III absorption bands of benzene, pyridine, pyrimidine, pyridazine, and *s*-tetrazine, and concluded that the absorption is shifted progressively to the red with each additional nitrogen atom, the effect being most marked when the nitrogen atoms are adjacent.

The published curves for quinoline, *iso*quinoline, and quinazoline (Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181; Elderfield, Williamson, Gensler, and Kremer, *J. Org. Chem.*, 1947, **12**, 405) show the same three main regions of absorption as naphthalene. In each case the most marked difference between the homocyclic and the heterocyclic compounds is that the group-III region is considerably more intense for the aromatic azahydrocarbons than for naphthalene.

FIG. 1. FIG. 2.

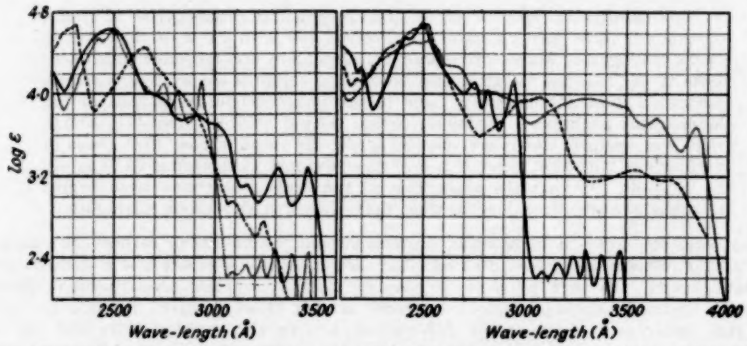


FIG. 1. *Absorption curves of phenanthrene* (.....) (*Mayneord and Roe*, 1935, loc. cit.), *o-phenanthroline* (III) (– – – – –), *and phenanthridine* (II) (———).

FIG. 2. *Absorption curves of phenanthrene* (———) (idem, ibid.), **3 : 4-*benzocinnoline*** (IV) (– – – – –), *and* **3 : 4-*benzocinnoline* N-*oxide*** (.....).

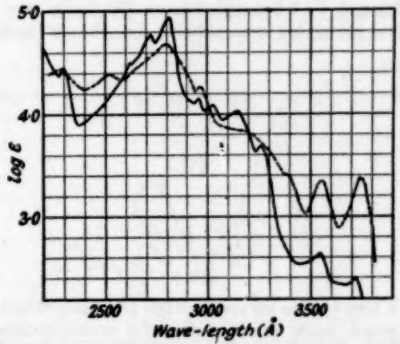
Phenanthrene also shows three main regions of absorption, at about 2500, at 2930—2750, and at 3140—3450 Å (Mayneord and Roe, *Proc. Roy. Soc.*, 1935, *A*, **152**, 299). Only one aromatic azahydrocarbon having the same ring system, namely, 5 : 6-benzoquinoline (I), seems to have been examined previously (Johnson, Woroch, and Mathews, *J. Amer. Chem. Soc.*, 1947, **69**, 566), but the spectra of several other representatives of this class, phenanthridine (II), *o*-phenanthroline (III), 3 : 4-benzocinnoline (IV), and 3 : 4-benzocinnoline *N*-oxide, have now been examined. The curves for (I), (II), and (III) (Fig. 1) are all very similar to that of phenanthrene, and show the same three regions of absorption. However, the maxima of the absorption bands in each region are shifted to shorter wave-lengths with each replacement of a methine group by a nitrogen atom. The group-I maximum for phenanthrene is at 2507 Å, but that for 5 : 6-benzoquinoline is at 2350 Å, and that for *o*-phenanthroline at 2310 Å.

(I.) (II.) (III.) (IV.)

The spectra of the cinnolines seem to be different in this respect (Fig. 2) for there is very little if any shift in the positions of the group-I maxima to shorter wave-lengths. As a matter

of fact, the chief point of interest in the curve for (IV) is that the absorption begins (about 4100 Å) at longer wave-lengths than for phenanthrene (3500 Å). This effect always seems to be most marked with compounds having two adjacent nitrogen atoms. The absorption spectrum of 3 : 4-benzocinnoline *N*-oxide (Fig. 2) is also of interest. The formation of the *N*-oxide involves the nitrogen " lone pair," and not the π electrons, so its absorption spectrum would be expected to resemble that of the parent compound about as closely as any substituted compound resembles a parent ring system, and this is found to be the case. The most note-

FIG. 3.



Absorption curves of 3 : 4-*benzophenanthrene* (———) (*Mayneord and Roe*, Proc. Roy. Soc., 1937, *A*, **158**, 634) *and of* 1′-*aza*-3 : 4-*benzophenanthrene* (V) (– – – – – –).

FIG. 4. FIG. 5.

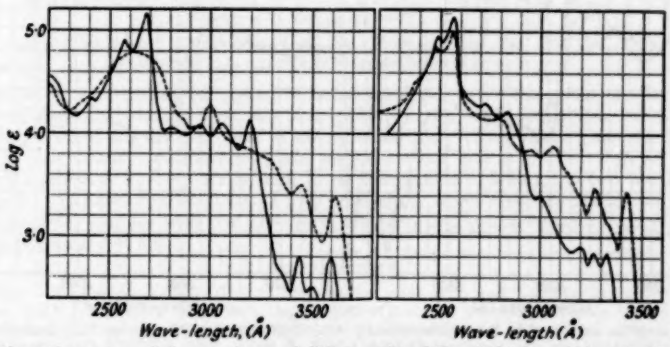


FIG. 4. *Absorption curves of chrysene* (———) (*Mayneord and Roe*, 1935, loc. cit.) *and of* 1-*azachrysene* (– – – – –).

FIG. 5. *Absorption curves of triphenylene* (———) (*Clar and Lombardi*, Ber., 1932, **65**, 1411) *and of* 1-*azatriphenylene* (VII) (– – – – – –)

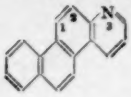
worthy difference is that the group-III bands are even more intense in the oxide than in the parent substance. The group-III absorption of 3 : 4-benzocinnoline itself, as well as that of all the other aromatic tricyclic azahydrocarbons examined, is about ten times more intense than that of phenanthrene.

There are several benzophenanthrenes, namely, 3 : 4-benzophenanthrene, 1 : 2-benzanthracene, chrysene, and triphenylene, and all have absorption spectra somewhat similar to that of phenanthrene except that the bands are shifted to longer wave-lengths. The same is true of the aza-derivatives. The spectrum of 1′-aza-3 : 4-benzophenanthrene (V) resembles that of 3 : 4-benzophenanthrene very closely (Fig. 3). The maxima in the group-I and group-III regions are almost identical, but the intensity of the group-III bands for the azahydrocarbon

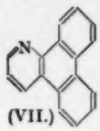
is again about ten times that for 3 : 4-benzophenanthrene (see also Johnson, Woroch, and Mathews, *loc. cit.*). Similarly, the spectrum of 3-azachrysene (VI) resembles that of chrysene (Fig. 4). There is considerable loss of fine structure, it is true, and again the intensity of the group-III region is about ten times that for the hydrocarbon (see also *idem, ibid.*). The spectrum of 1-azatriphenylene (VII) is likewise closely related to that of the hydrocarbon (Fig. 5), the group-III region again being more intense in the case of the azahydrocarbon.

The spectrum of 1 : 2-benzanthracene exhibits three groups of absorption bands, with twelve peaks in all, and has already been fairly extensively investigated (Jones, *J. Amer. Chem. Soc.*, 1940, **62**, 148; Badger and Pearce, *loc. cit.*). 3 : 4-Benzacridine (VIII), 5-aza-1 : 2-benzanthracene (IX), and 1 : 2-benzophenazine (X) have now been examined (Figs. 6 and 7), and the same general principles seem to hold; *i.e.*, the curves show a general resemblance

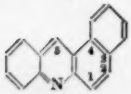
(V.)



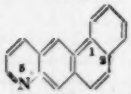
(VI.)



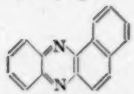
(VII.)



(VIII.)



(IX.)



(X.)

to one another, there is a loss of fine structure with the azahydrocarbons, and the group-III region of absorption is much more intense with the azahydrocarbons than for 1 : 2-benzanthracene itself. Moreover, the absorption of the diaza-compound, 1 : 2-benzophenazine,

FIG. 6. FIG. 7.

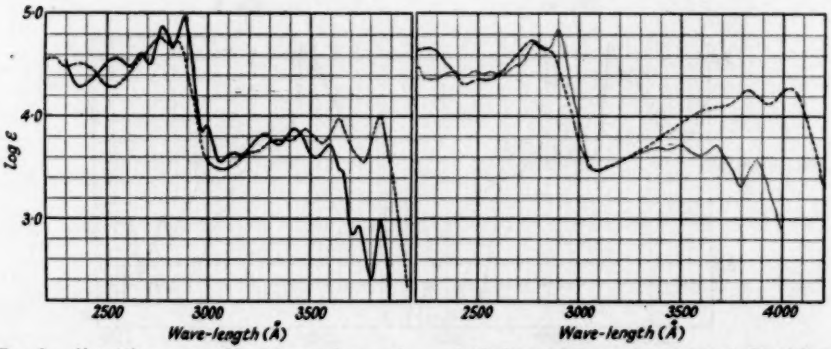


FIG. 6. *Absorption curves of* 1 : 2-*benzanthracene* (———) (*Badger and Pearce*, loc. cit.) *and of* 3 : 4-*benzacridine* (– – – – –).

FIG. 7. *Absorption curves of* 1 : 2-*benzophenazine* (X) (– – – – –) *and of* 5-*aza*-1 : 2-*benzanthracene* (IX) (. . . . .).

begins at a longer wave-length than that of the hydrocarbon, and this substance is pale yellow whereas the hydrocarbon is colourless.

Unlike the compounds already mentioned, anthracene has only two regions of absorption. The first (group-I bands) at about 2515 Å corresponds to the benzene absorption at about 1790 Å. The second (group-II) extends from about 3000 to about 3750 Å, and corresponds to the benzene absorption in the 2000 Å region. The group-III bands of anthracene, corresponding to the 2500 Å region of benzene, are hidden under the group-II bands, for, as Clar (*loc. cit.*) has shown, the group-II bands move more to the red for every additional linear benzene ring than do the group-III bands. Four heterocyclic analogues of anthracene have now been examined: acridine, 1-aza-anthracene, 2-aza-anthracene, and phenazine (see Figs. 8 and 9).

There are very close resemblances between the curves but the intensities of the group-II regions in acridine and phenazine are about twice that in the hydrocarbon. It is also noteworthy that the absorption of the azahydrocarbons, especially of phenazine, begins at longer wave-lengths than for anthracene. For this reason phenazine is pale yellow but anthracene and acridine are colourless.

It seems reasonable to conclude from the above survey that, in general, the absorption spectra of the azahydrocarbons closely resemble those of their carbocyclic analogues. The chief differences seem to be: (i) that the group-III absorption bands are much more intense than those of the hydrocarbons; (ii) that in anthracene analogues (which do not exhibit group-III absorption), the group-II bands of the azahydrocarbons are sometimes slightly more intense than those of the hydrocarbon; (iii) that there is a considerable loss of fine structure in replacing

FIG. 8. FIG. 9.

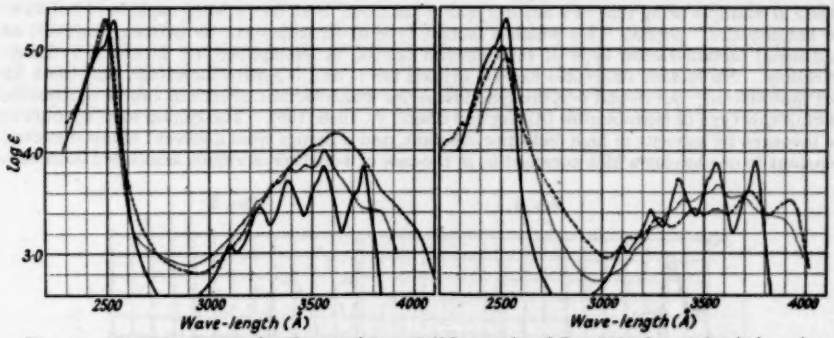


FIG. 8. *Absorption curves of anthracene* (———) (*Mayneord and Roe*, 1935, loc. cit.), *of phenazine* (– – – – –), *and of acridine* (. . . . .).

FIG. 9. *Absorption curves of anthracene* (———) (*Mayneord and Roe*, 1935, loc. cit.), *of* 1-*aza-anthracene* (. . . . .), *and of* 2-*aza-anthracene* (– – – – –).

CH groups by N, but that as far as can be ascertained the various maxima are not shifted to any marked extent; and (iv) that the absorption of the azahydrocarbons often begins at slightly longer wave-lengths than that of the hydrocarbons. This effect is not very apparent, if at all, in compounds containing only one nitrogen atom, but is marked with all the diaza-compounds examined, and especially with those compounds in which the two nitrogen atoms are adjacent. These differences being borne in mind, it seems that the absorption spectra of the hydrocarbons can be used for structure identification purposes with azahydrocarbons, with little possibility of error.

EXPERIMENTAL.

Materials.—We are indebted to Dr. A. Etienne for gifts of 1- and 2-aza-anthracene (cf. Etienne, *Ann. Chim.*, 1946, **1**, 5), and to Dr. E. Mosettig for gifts of 5-aza-1 : 2-benzanthracene, 1-azatriphenylene, 3-azachrysene, and 1'-aza-3 : 4-benzophenanthrene (cf. Mosettig and Krueger, *J. Org. Chem.*, 1938, **3**, 317; Krueger and Mosettig, *ibid.*, 1940, **5**, 313). 1 : 2-Benzophenazine was prepared by Ullmann and Heisler's method (*Ber.*, 1909, **42**, 4263), and purified by sublimation in a high vacuum and recrystallisation from acetic acid. The preparations of the 3 : 4-benzocinnoline, 3 : 4-benzocinnoline *N*-oxide, 3 : 4-benzacridine, and of the phenanthridine used are described in Part III (*J.*, 1951, 3207); the other materials were obtained commercially.

Absorption Spectra.—Spectra were determined with a Beckman DU spectrophotometer, absolute alcohol being used as solvent. The absorption curves of the parent hydrocarbons given in the figures are those recorded in the literature, and have usually been determined with other instruments. In many cases, however, we have re-examined the spectra, using the Beckman instrument, and have obtained curves in good agreement with the original workers.

We are grateful to Dr. A. Etienne and to Dr. E. Mosettig for gifts of materials, and to the Director of Chemistry (Mr. R. J. Cowan), South Australian Government Department of Chemistry, for permission to use the Beckman spectrophotometer. We are also indebted to the Commonwealth Government Research Fund for maintenance grants (to R. S. P. and R. P.).

JOHNSON CHEMICAL LABORATORIES, UNIVERSITY OF ADELAIDE. [*Received, May, 15th*, 1951.]

705. *Polynuclear Heterocyclic Systems. Part II.* Hydroxy-derivatives.*

By G. M. Badger, R. S. Pearce, and R. Pettit.

Phenazin-2-ol and 3 : 4-dihydroxy-1 : 2-benzophenazine (I) have been shown to exhibit lactam–lactim tautomerism. Phenazin-1-ol, on the other hand, does not undergo tautomerisation, and it is suggested that this substance is stabilised in the lactim form by hydrogen bonding between the hydroxyl group and the adjacent nitrogen atom.

Tautomerism of the keto–enol type has often been encountered in carbocyclic phenols, the classical example being that of 9-anthrol $\rightleftharpoons$ 9-anthrone, both forms being capable of isolation. In heterocyclic "phenols" for which a lactam type of structure can be written, however, an additional lactam–lactim type of tautomerism occurs, as exemplified by 2- and 4-hydroxypyridines. No lactam structures can be written for 1- and 3-hydroxyacridines, and these do not tautomerise; but 2- and 4-hydroxyacridines, for which lactam structures can be written, do exhibit this type of tautomerism (Albert and Short, *J.*, 1945, 760). The lactam form appears to be favoured by solvents of high dielectric constant, and a change from a solvent of low dielectric constant to one having a high constant is, in the case of 4-hydroxyacridine, associated both with

Fig. 1. Fig. 2.

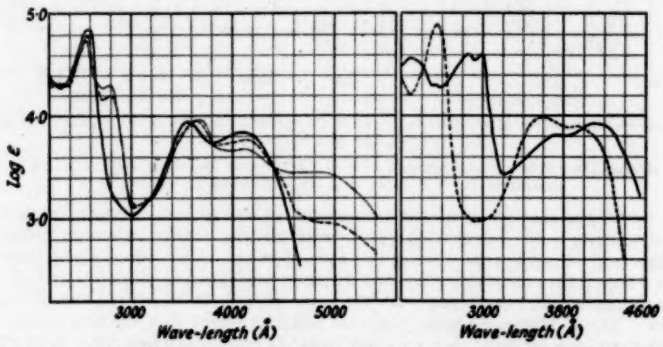


Fig. 1. *Absorption spectra of phenazin-2-ol in absolute alcohol* (———), *in* 50% (*v*/*v*) *ethanol* (– – – – –), *and in water* (. . . . .).

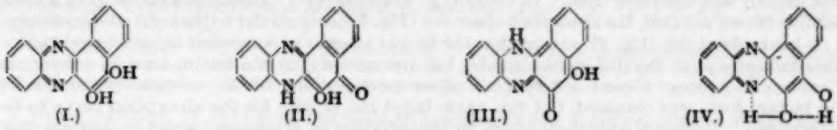
Fig. 2. *Absorption spectra of* 3 : 4-*dimethoxy*-1 : 2-*benzophenazine* (———) *and of* 2-*methoxyphenazine* (– – – – –), *both in absolute alcohol.*

a considerable deepening in the colour of the solution and with increased absorption at long wave-lengths. Lactam–lactim structures can be written for phenazin-1- and -2-ol, and the present investigation was suggested by the observation that although these are both yellow solids resembling phenazine in colour, yet 3 : 4-dihydroxy-1 : 2-benzophenazine (I) is a deep blue-violet solid quite unlike its pale yellow parent substance, 1 : 2-benzophenazine. It therefore seemed of interest to examine the colour of these substances in solution, and also to determine their absorption spectra.

It has been found that phenazin-2-ol does show lactam–lactim tautomerism. It gave a yellow solution in alcohol and its absorption spectrum in this solvent (Fig. 1) closely resembles that of 2-methoxyphenazine in the same solvent (Fig. 2). It may be concluded therefore that phenazin-2-ol exists predominantly in the lactim form in absolute alcohol. In aqueous solvents, however, a deeper colour was apparent, and this is associated with increased absorption at long wave-lengths. In pure water, for example, phenazin-2-ol gave an orange solution, and the absorption extended as far as 5400 Å. Indeed, the curve in this solvent shows some similarities

* Part I, preceding paper.

(Fig. 3) to that of phenothiazone which, of course, has a pure lactam structure. The situation clearly approximates to that observed by Albert and Short (*loc. cit.*) for 2-hydroxyacridine, and there seems no reason to doubt that the lactam form is favoured by the high dielectric constant of aqueous solvents, as suggested by these authors.



In contrast to the above, phenazin-1-ol does not seem to exhibit lactam–lactim tautomerism in spite of the facts that a lactam structure can be drawn and the analogous 4-hydroxyacridine shows the effect very clearly. Phenazin-1-ol gave a pale yellow solution in absolute alcohol and its colour was unchanged by dilution with water. Moreover, the absorption spectrum in aqueous alcohol was identical (within experimental error) with that in absolute alcohol (Fig. 4), and similar to that of phenazine itself. The lactam form is therefore unimportant with this compound, at least under the conditions studied : the most reasonable explanation would seem to be that its lactim form is stabilised by hydrogen bonding to the adjacent nitrogen, and this

FIG. 3. FIG. 4.

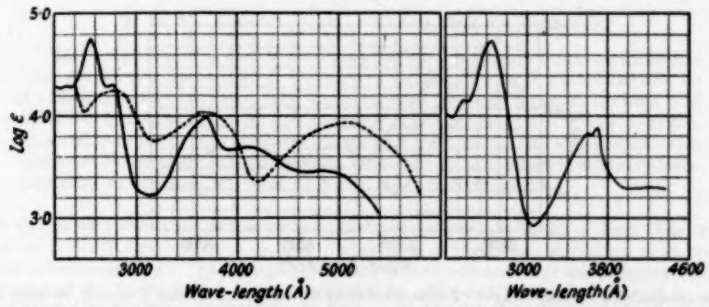


FIG. 3. *Absorption spectra of phenazin-2-ol in water* (———) *and of phenothiazone in alcohol* (– – – – –).

FIG. 4. *Absorption spectrum of phenazin-1-ol in absolute alcohol.*

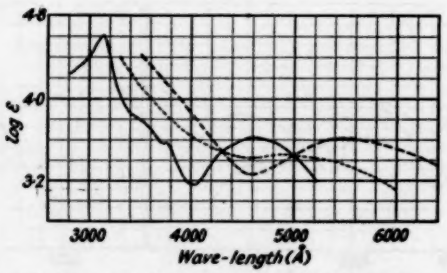
has been confirmed by an examination of the infra-red absorption spectrum of this compound kindly carried out for us by Dr. J. B. Willis of the Division of Industrial Chemistry, C.S.I.R.O., Melbourne. The substance was examined in the 1500—1800 cm.$^{-1}$ region as a " Nujol " mull, but no band corresponding to the normal carbonyl frequency (about 1670 cm.$^{-1}$) was found, so the lactam form appears to be excluded. It was also examined in the 3000—3600 cm.$^{-1}$ region as a dilute solution in carbon tetrachloride, a sharp band at 3445 cm.$^{-1}$ being found. As the normal frequency of the OH vibration is 3600—3650 cm.$^{-1}$, and that of the NH vibration is 3400—3500 cm.$^{-1}$, the results appear to indicate weak hydrogen bonding between the OH and the ring nitrogen in the lactim form. Albert and Goldacre (*J.*, 1943, 454) have suggested that hydrogen bonding occurs in the related compounds 1-hydroxy- and 1-amino-acridine, and it has often been suggested that similar hydrogen bonding occurs in the closely related compound 8-hydroxyquinoline. In this connection it is noteworthy that 8-hydroxyquinoline is volatile in steam and that its m. p. is well over 100° below that of any of the isomeric hydroxyquinolines.

Lactam–lactim tautomerism has also been confirmed with 3 : 4-dihydroxy-1 : 2-benzophenazine (I), and the blue colour of this substance in the solid state probably indicates that the compound exists predominantly as the lactam (II). The alternative lactam structure (III) is probably unimportant, for it involves an unstable 2 : 3-naphthaquinone type of bond structure. In absolute alcohol 3 : 4-dihydroxy-1 : 2-benzophenazine gives a brown solution, which however gradually fades to pale yellow in a few days. This change is caused by oxidation, the diol being converted into the yellow 1 : 2-benzophenazine-3 : 4-quinone. A freshly prepared solution became dark blue on dilution with water, evidently indicating the formation of an

increased quantity of the lactam form (II), but this blue colour faded in a few minutes, the quinone again being formed by oxidation. The lactam form (II) is evidently very readily oxidised to the quinone by dissolved oxygen in the solvent. It was impossible to obtain a sufficiently concentrated alcoholic solution of this substance for accurate spectrographic work, and dioxan was therefore tried. In dioxan, 3 : 4-dihydroxy-1 : 2-benzophenazine gave a dark reddish-brown solution, the absorption spectrum (Fig. 5) being similar to that of 3 : 4-dimethoxy-1 : 2-benzophenazine (Fig. 2), except that the former absorbs at somewhat longer wave-lengths. This indicates that the diol exists largely, but not entirely, in the lactim form in anhydrous dioxan. In aqueous dioxan a deep blue colour corresponding to the increased proportion of the lactam form was obtained, but this again faded too rapidly for the absorption curve to be determined. Recourse had to be made to the addition of a reducing agent to prevent this oxidation, and the spectrum was therefore determined in aqueous dioxan containing a little hydrazine. The curves show the increased absorption at long wave-lengths, and the existence of the isosbestic points at 4300 Å and at 5000 Å probably indicates that the addition of hydrazine has not upset the position of the equilibrium.

The tendency of 3 : 4-dihydroxy-1 : 2-benzophenazine to exist largely in the lactam form (II) is of some interest. Weak hydrogen bonding both between the hydroxyl groups and between the 4-hydroxyl group and the ring nitrogen atom might be expected (cf. Pauling, " The Nature of the Chemical Bond," 2nd edn., 1940, p. 325; Albert and Goldacre, *loc. cit.*). Unlike the case of phenazin-1-ol, however, this hydrogen bonding (IV) would facilitate the formation

FIG. 5.



Absorption spectra of 3 : 4-*dihydroxy*-1 : 2-*benzophenazine in anhydrous dioxan* (———), *in* 80% *aqueous dioxan containing* 1·15% *of hydrazine* (– – – – –), *and in* 50% *aqueous dioxan containing* 1·15% *of hydrazine* (— — —).

of the lactam. No doubt the lactam form (II) is also favoured by the fact that it contains an α-naphthaquinonoid structure which is much more stable than the *o*- and *p*-benzoquinonoid structures of the lactam forms of phenazin-1- and -2-ol, respectively.

EXPERIMENTAL.

Phenazin-1-ol.—This material was kindly supplied by Dr. B. Hegedüs, of F. Hoffmann-La Roche & Co., Basle (cf. Hegedüs, *Helv. Chim. Acta*, 1950, **33**, 766).

Phenazin-2-ol and 2-Methoxyphenazine.—Both compounds were kindly supplied by Dr. D. L. Vivian of the National Institute of Health, U.S.A. (compare Vivian, *J. Amer. Chem. Soc.*, 1949, **71**, 1139).

Phenothiazone.—This was prepared according to Dutch Patent, 59,559 (*Chem. Abs.*, 1947, **41**, 5557), and recrystallised from water.

3 : 4-*Dihydroxy*-1 : 2-*benzophenazine.*—A solution of 1 : 2-benzophenazine-3 : 4-quinone (Fischer and Schindler, *Ber.*, 1906, **39**, 2238) (2 g.) in chloroform (250 c.c.) at 40° was treated with phenylhydrazine (25 c.c.). A blue-violet precipitate immediately formed, and the product was collected after ½ hour. For analysis it was recrystallised from ethyl acetate and washed with acetone. It formed small violet-blue needles, m. p. indefinate at 270° (Found : C, 73·0; H, 3·9. Calc. for $C_{16}H_{10}O_2N_2$: C, 73·3; H, 3·85%) (Zincke and Wiegand, *Annalen*, 1895, **286**, 58, give m. p. 241°; Fischer, *Ber.*, 1903, **36**, 3622, gives m. p. 270°, after sintering at 240°).

3 : 4-*Diacetoxy*-1 : 2-*benzophenazine.*—This was prepared by boiling the above dihydroxy-compound with acetic anhydride. It was remarkably unstable. In the presence of a little water, or even with acetic acid, hydrolysis took place and the recrystallisation liquors always became deep red-brown. It was successfully recrystallised from acetic anhydride, the slight amount of colour in the liquors being removed with cold acetic anhydride. 3 : 4-Diacetoxy-1 : 2-benzophenazine formed beautiful pale yellow

blades, m. p. 214—216° (Found : C, 69·5; H, 4·1. Calc. for $C_{20}H_{14}O_4N_2$: C, 69·4, H, 4·1%). Zincke and Wiegand (*Annalen*, *loc. cit.*) give m. p. 208°.

3 : 4-*Dimethoxy*-1 : 2-*benzophenazine*.—3 : 4-Dihydroxy-1 : 2-benzophenazine was methylated at 90°, by the alternate addition of sodium hydroxide solution and methyl sulphate, in the usual way. After several recrystallisations from acetic acid, and then from alcohol (charcoal), **3 : 4-*dimethoxy*-1 : 2-*benzophenazine*** formed canary-yellow needles, m. p. 160—161° (Found : C, 74·5; H, 4·6. $C_{18}H_{14}O_2N_2$ requires C, 74·5; H, 4·9%).

Absorption Spectra.—For rapidity, the spectra of 3 : 4-dihydroxy-1 : 2-benzophenazine in aqueous dioxan were determined with a Bellingham and Stanley spectrophotometer fitted with a Hilger echelon cell and rotating sector. All other spectra were determined with a Beckman DU spectrophotometer.

We are grateful to Dr. B. Hegedüs and to Dr. D. L. Vivian for gifts of phenazinols, and we also thank the Director of Chemistry (Mr. R. J. Cowan), South Australian Government Department of Chemistry, for permission to use the Beckman spectrophotometer. Microanalyses were carried out by Mr. R. T. Howard. We are also indebted to the Commonwealth Government Research Fund for maintenance grants (to R. S. P. and R. P.).

JOHNSON CHEMICAL LABORATORIES, UNIVERSITY OF ADELAIDE. [*Received, May 15th*, 1951.]

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706. *Polynuclear Heterocyclic Systems. Part III.* The 3 : 4-Benzacridine–5 : 10-Dihydro-3 : 4-benzacridine Complex.*

By G. M. BADGER, J. H. SEIDLER, and B. THOMSON.

The reduction of 3 : 4-benzacridone with lithium aluminium hydride has been shown to give an orange molecular complex of 3 : 4-benzacridine and its 5 : 10-dihydro-derivative. The same reagent reduced phenanthridone and 9-chlorophenanthridine to 9 : 10-dihydrophenanthridine, which was dehydrogenated over palladium to phenanthridine in good yield. 3 : 4-Benzocinnoline has been obtained by reduction of its *N*-oxide with lithium aluminium hydride, and also, in one step, by reduction of 2 : 2′-dinitrodiphenyl.

ONE of the most interesting properties of phenazine is that it forms a deep blue crystalline complex with dihydrophenazine. Certain derivatives of phenazine also form such complexes, which have been known as "phenazhydrins," and it is significant that the complex formed from phenazine and 9 : 10-dihydro-1-methylphenazine is identical with that formed from 9 : 10-dihydrophenazine and 1-methylphenazine (Clemo and McIlwain, *J.*, 1934, 1991). Relatively few complexes of this nature have been reported, however, although "Morgan's base" has recently been shown to be a molecular complex of 3 : 4-6 : 7-dibenzacridine and 5 : 10-dihydro-3 : 4-6 : 7-dibenzacridine (Blout and Corley, *J. Amer. Chem. Soc.*, 1947, **69**, 763). The present paper records the ready preparation of an orange complex between 3 : 4-benzacridine (I) and its 5 : 10-dihydro-derivative.

The 3 : 4-benzacridine–5 : 10-dihydro-3 : 4-benzacridine complex was obtained by two different methods : (i) in quantitative yield by reduction of 3 : 4-benzacridone with lithium aluminium hydride, and (ii) by dehalogenation of 5-chloro-3 : 4-benzacridine with hydrogen and Raney nickel. In (ii) it was accompanied by the colourless 5 : 10-dihydro-3 : 4-benzacridine, from which it was separated by chromatography on alumina.

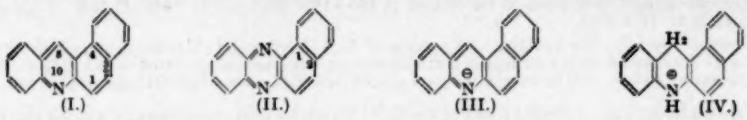
The nature of the complex follows from the following facts. When treated with hydrochloric acid, part of the material dissolved. The acid-insoluble part was identified as the (non-basic) 5 : 10-dihydro-3 : 4-benzacridine by comparison with an authentic specimen, and the acid-soluble part, after precipitation with alkali and recrystallisation from alcohol, was similarly identified as 3 : 4-benzacridine (I). Moreover, the orange complex was obtained without difficulty by mixing equimolecular quantities of 3 : 4-benzacridine and 5 : 10-dihydro-3 : 4-benzacridine, in alcoholic solution. Finally, the absorption spectrum of the complex (Fig. 1) shows that, like "phenazhydrin," it is dissociated into its components in alcoholic solution.

Clemo and McIlwain (*loc. cit.*) stated that acridine does not form a complex with acridan, and this observation has now been confirmed. Furthermore, a complex could not be obtained between phenanthridine and 9 : 10-dihydrophenanthridine. Attempts to prepare a complex between 1 : 2-benzophenazine (II) and 9 : 10-dihydro-1 : 2-benzophenazine were frustrated by

* Part II, preceding paper.

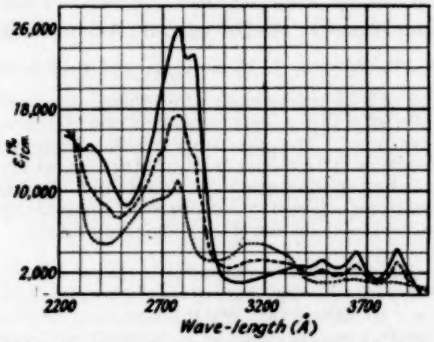
the fact that the latter appears to be unstable, all attempts at reduction of 1 : 2-benzophenazine yielding either unchanged material or a more highly reduced compound.

The available evidence indicates that complexes are formed only when the dihydro-compound has an optimum degree of stability, and the aromatic component an optimum degree of electro-



negativity. The complexes seem to be very closely related to the quinhydrones, and to be formed by electron transfer from the dihydro-compound to the aromatic compound (Weiss, *J.*, 1942, 245; 1943, 462; 1944, 464). The application of this concept to the 3 : 4-benzacridine–5 : 10-dihydro-3 : 4-benzacridine complex gives the two ions (III and IV). Each ion would be stabilised by resonance, and the complex can be pictured as being built up of successive layers of planar molecules having positive or negative charges " smeared out " over the whole of the conjugated systems, the molecules being held together by electrostatic attraction. The " phenaz-

FIG. 1.



Absorption spectra of 3 : 4-*benzacridine* (———), *of* 5 : 10-*dihydro*-3 : 4-*benzacridine* (– – – – –), *and of the complex* (. . . . .), *all in alcoholic solution. The spectra are plotted on a* $\epsilon^{1\%}_{1\,cm.}$ *scale and show four isosbestic points* (*at* 2280, 2950, 3350, *and* 3920 Å).

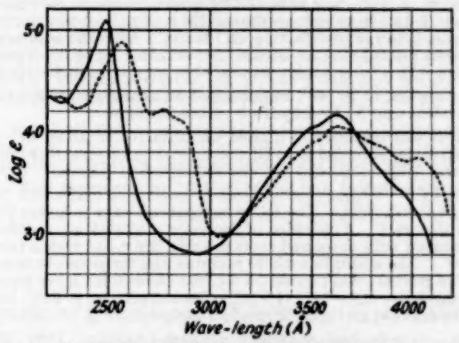
hydrins " are deeper in colour than the acridine complexes, and this seems reasonable in view of the fact that the former compounds have twice as many nitrogen atoms and increased possibilities of resonance.

For the preparation of 3 : 4-benzacridone and of 5-chloro-3 : 4-benzacridine, *o*-chlorobenzoic acid was first condensed with 2-naphthylamine (Bachman and Picha, *J. Amer. Chem. Soc.*, 1946, **68**, 1599), and the resulting naphthylanthranilic acid cyclised. 3 : 4-Benzacridone was obtained by Ullmann's method (*Annalen*, 1907, **355**, 312), but 5-chloro-3 : 4-benzacridine was obtained directly by use of phosphorus oxychloride. As already mentioned, dehalogenation with hydrogen and Raney nickel gave a mixture of the 3 : 4-benzacridine–5 : 10-dihydro-3 : 4-benzacridine complex and 5 : 10-dihydro-3 : 4-benzacridine. The latter was smoothly oxidised to 3 : 4-benzacridine with dichromate (compare Albert and Willis, *J. Soc. Chem. Ind.*, 1946, **65**, 26), and the present synthesis of this compound constitutes a distinct improvement on Ullmann's method (*loc. cit.*).

Several methods for the preparation of phenanthridone were investigated. The Schmidt reaction on fluorenone (Walls, *J.*, 1935, 1405; Smith, *J. Amer. Chem. Soc.*, 1948, **70**, 320) gave a good yield, but the method is not very suitable on a large scale. The same criticism applies to the formation of phenanthridone by the action of hydrazoic acid on diphenic acid, although the yield is good (cf. Caronna, *Gazzetta*, 1941, **71**, 475; Stephenson, *J.*, 1949, 2620). The most satisfactory method proved to be that of Oyster and Adkins (*J. Amer. Chem. Soc.*, 1921, **43**, 208) involving the conversion of diphenic acid into its anhydride, and then into diphenamic acid and phenanthridone.

There seems to be no really satisfactory method for the conversion of phenanthridone into phenanthridine on a large scale. Albert, Brown, and Duewell (*J.*, 1948, 1284) obtained phenanthridine by dehalogenation of 9-bromophenanthridine with hydrogen and Raney nickel, and it seemed that a modification of this method would be suitable. Accordingly, 9-chlorophenanthridine was prepared by an improved process involving the addition of dimethylaniline to the reaction mixture; but all attempts to dehalogenate this compound either with very " reactive " Raney nickel (Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 695) and hydrogen, or with catalyst prepared by the ordinary method (*Org. Synth.*, 1941, **21**, 15) and " aged " for some weeks, gave 9 : 10-dihydrophenanthridine. Attempts to interrupt the hydrogenation did not give satisfactory results. Another dehalogenation method tried involved the use of toluene-*p*-sulphonhydrazide, as suggested by Albert and Royer (*J.*, 1949, 1148) for the dehalogenation of 5-chloroacridines. The method proved rather unsatisfactory in this case, and phenanthridine was obtained in only 30% yield. The use of lithium aluminium hydride was also investigated. 9-Chlorophenanthridine was reduced to 9 : 10-dihydrophenanthridine with lithium aluminium hydride, and the reduction of phenanthridone to dihydrophenanthridine proceeded very smoothly and in good yield. At first sight the latter result appears to be at variance with the work of de Mayo and McKee (*Nature*, 1950, **166**, 1075), who obtained phenanthridine on reduction of phenanthridone with lithium aluminium hydride. However,

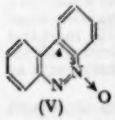
FIG. 2.



Absorption spectra of 1′ : 2′ : 3′ : 4′-*tetrahydro*-1 : 2-*benzophenazine* (– – – – –) *and of phenazine* (———), *both in alcoholic solution.*

these workers evidently used only the theoretical quantity of lithium aluminium hydride. In the present work, a large excess was used, and the fact that dihydrophenanthridine was obtained is in agreement with the work of Wooten and McKee (*J. Amer. Chem. Soc.*, 1949, **71**, 2946), who found that phenanthridine is reduced to 9 : 10-dihydrophenanthridine under these conditions. In no case was evidence of a phenanthridine–dihydrophenanthridine complex noted, and a complex was not formed by crystallisation from a solution containing equimolecular quantities of the two substances.

Lithium aluminium hydride has also been used in some synthetical experiments leading to 3 : 4-benzocinnoline. This substance had previously been obtained in one stage by electrolytic reduction of 2 : 2′-dinitrodiphenyl (Wohlfart, *J. pr. Chem.*, 1902, **65**, 295). It has also been obtained previously by a two-stage reduction of the same substance. The reduction to the *N*-oxide (V) was carried out with sodium sulphide, and this was reduced to 3 : 4-benzocinnoline with stannous chloride and hydrochloric acid (Ullmann and Dieterle, *Ber.*, 1904, **37**, 23; King and King, *J.*, 1945, 824). In our hands the latter process gave only indifferent results, but the reduction of benzocinnoline *N*-oxide was effected without difficulty by using zinc dust and acetic acid. It has also been found that 2 : 2′-dinitrodiphenyl is smoothly reduced to 3 : 4-benzocinnoline with lithium aluminium hydride, and the same reagent also reduced 3 : 4-benzocinnoline *N*-oxide, in good yield.



(V)

Many attempts were made to obtain 9 : 10-dihydro-1 : 2-benzophenazine. Unchanged material was recovered after attempted reduction with sodium and methyl alcohol, sodium and *iso*amyl alcohol, ammonium sulphide, sodium sulphide, and lithium aluminium hydride. With

hydrogen and Raney nickel, however, reduction took place to give 1′ : 2′ : 3′ : 4′-tetrahydro-1 : 2-benzophenazine, and the same tetrahydro-derivative was obtained by reduction with hydrogen and palladium. The structure of this compound follows from the similarity of its absorption spectrum (Fig. 2) to that of phenazine.

Experimental.

The 3 : 4-*Benzacridine*–5 : 10-*Dihydro*-3 : 4-*benzacridine Complex*.—(i) 5-Chloro-3 : 4-benzacridine (5 g.; prepared by Bachman and Picha's method, *loc. cit.*) was suspended in absolute ethanol (150 c.c.), and potassium hydroxide (1·5 g.) and Raney nickel catalyst (3·5 g.) were added. After hydrogenation in the usual way the alcoholic solution was separated from the catalyst and concentrated to 80 c.c. Water was added to the boiling solution until crystallisation started, and pale yellow flakes (2·5 g.) of 5 : 10-dihydro-3 : 4-benzacridine which separated were collected. Similar treatment of the mother-liquor gave bright orange crystals (1·5 g.) not identical with the above. These were dissolved in benzene and the solution was passed through a column of alumina. The column was developed and eluted with chloroform, an orange band being the first to pass through the column. Removal of the solvent and recrystallisation from aqueous alcohol gave the *complex* as orange needles, m. p. 140° (Found: C, 88·5; H, 5·2. $C_{34}H_{24}N_2$ requires C, 88·7; H, 5·2%). A portion of this compound was treated with concentrated hydrochloric acid and water (1 : 1), and the suspension warmed. The insoluble part was recrystallised from aqueous alcohol. It formed very pale yellow crystals, m. p. 165°, alone or mixed with authentic 5 : 10-dihydro-3 : 4-benzacridine (Lehmstedt, Bruns, and Klee, *Ber.*, 1936, **69**, 2399, give m. p. 158° for this substance). The acid solution was basified with ammonia, and the colourless precipitate recrystallised from aqueous alcohol. It formed colourless crystals, m. p. 130—131°, alone or mixed with authentic 3 : 4-benzacridine.

(ii) The same complex, m. p. 140°, was obtained by gradual addition (40 minutes) of a suspension of lithium aluminium hydride (0·2 g.) in anhydrous dioxan (15 c.c.) to 3 : 4-benzacridone (0·25 g.; Ullmann, *loc. cit.*) in anhydrous dioxan, followed by refluxing for 7 hours. After the addition of water to decompose the complex, the mixture was filtered and the filtrate concentrated. The crude product was recrystallised from aqueous alcohol, from which the complex separated in almost quantitative yield.

(iii) The same orange complex, m. p. 140°, was obtained on mixing ethanolic solutions of equimolecular quantities of 3 : 4-benzacridine and 5 : 10-dihydro-3 : 4-benzacridine.

3 : 4-*Benzacridine*.—This was obtained in almost quantitative yield by the oxidation of the crude 5 : 10-dihydro-3 : 4-benzacridine, obtained as in (i) above, with potassium dichromate and sulphuric acid as described by Albert and Willis (*loc. cit.*) for the oxidation of acridan. 3 : 4-Benzacridine formed colourless needles from aqueous alcohol, and had m. p. 131°, in agreement with Ullmann (*loc. cit.*).

Phenanthridone from Diphenic Acid.—The following method gave a better yield of phenanthridone than that of Stephenson (*loc. cit.*). A mixture of diphenic acid (2·4 g.), sulphuric acid (20 c.c.), and chloroform (40 c.c.) was treated with powdered sodium azide (2·6 g.) at such a rate that the temperature was maintained at 45—50°. The addition took 30 minutes, the temperature being kept at 50° ± 2° for a further 80 minutes. The mixture was poured on ice, the chloroform layer separated and evaporated, and the insoluble phenanthridone, m. p. 287° (1·1 g.), collected (lit., m. p. 293°, corr.). The acid filtrate was basified with sodium hydroxide, giving 2 : 2′-diaminodiphenyl, m. p. 80—80·5° (0·3 g.) (lit., m. p. 81°).

9-*Chlorophenanthridine*.—Graebe and Wander's method (*Annalen*, 1893, **276**, 245) proved very tedious and gave only small yields of the desired compound. The following method proved satisfactory, however, and gave almost quantitative yields. A mixture of phenanthridone (19 g.), phosphorus oxychloride (150 c.c.), and dimethylaniline (6 c.c.) was refluxed for 3 hours (compare Kenner *et al.*, *J.*, 1943, 574). The excess of phosphorus oxychloride was removed *in vacuo*, and the residue poured on ice. The product was extracted with ether, and the ethereal solution washed with sodium carbonate, dried, and evaporated. The residual 9-chlorophenanthridine had m. p. 116° after recrystallisation from aqueous alcohol.

9 : 10-*Dihydrophenanthridine*.—(i) A mixture of 9-chlorophenanthridine (1·0 g.), potassium hydroxide (0·5 g.), and Raney nickel catalyst (1·5 g.) in alcohol (30 c.c.) was shaken with hydrogen at room temperature and pressure. When hydrogenation became very slow the solution was separated from the catalyst, concentrated to a small volume, and treated with a little water. The material which separated was recrystallised from alcohol, giving 9 : 10-dihydrophenanthridine (0·83 g.) as colourless plates, m. p. 125° (de Diesbach and Aeschbach, *Helv. Chim. Acta*, 1945, **28**, 1396, give m. p. 125°) (Found: C, 86·4; H, 6·0. Calc. for $C_{13}H_{11}N$: C, 86·2; H, 6·2%).

(ii) A suspension of lithium aluminium hydride (0·5 g.) in dioxan (15 c.c.) was gradually added to a boiling suspension of phenanthridone (0·5 g.) in anhydrous dioxan (30 c.c.). The refluxing was continued for 8 hours, after which water was added to decompose the complex. After removal of the inorganic material by filtration, the liquors were diluted with water, and the product collected and recrystallised from aqueous alcohol. The dihydrophenanthridine (0·4 g.) was identified by direct comparison with an authentic specimen prepared as above.

(iii) 9 : 10-Dihydrophenanthridine was also obtained by reduction of 9-chlorophenanthridine with lithium aluminium hydride.

Phenanthridine.—(i) Dehydrogenation of 9 : 10-dihydrophenanthridine (1·0 g.) was effected by palladised charcoal at 260° (20 minutes). The resulting phenanthridine, crystallised from aqueous alcohol, formed fine white needles (0·93 g.), m. p. 106° (Albert, Brown, and Duewell, *loc. cit.*, give m. p. 107—108°).

(ii) Dry hydrogen chloride was passed into a solution of toluene-*p*-sulphonhydrazide (1·5 g.) and 9-chlorophenanthridine (1·0 g.) in chloroform (20 c.c.). After 3 days at room temperature the yellow precipitate was collected and added to a solution of sodium hydroxide (4·0 g.) in water (30 c.c.) and

ethylene glycol (80 c.c.). The mixture was heated on the water-bath for 3½ hours, poured into water (200 c.c.), and kept in the refrigerator overnight. The resulting precipitate was collected and dissolved in acid, from which the phenanthridine separated on basification. Purification from aqueous alcohol gave phenanthridine, m. p. 106°, in 30% yield.

3 : 4-*Benzocinnoline.*—A mixture of benzocinnoline *N*-oxide (5·0 g.; King and King, *loc. cit.*) in glacial acetic acid (50 c.c.) was heated very gently, and zinc dust (5 g.) added slowly during 5 minutes. After being heated for a further 10 minutes the solution was filtered and the filtrate poured into ammonia. The resulting 3 : 4-benzocinnoline (4·3 g.) separated from benzene as pale yellow blades, m. p. 156° in agreement with Ullmann and Dieterle (*loc. cit.*).

(ii) A solution of lithium aluminium hydride (3·0 g.) in anhydrous ether (15 c.c.) was added to a solution of 2 : 2′-dinitrodiphenyl (4·0 g.) in anhydrous benzene (35 c.c.), and the mixture refluxed for 4 hours. A brown precipitate formed during the reaction. Water (5 c.c.) was added to the cold solution, the inorganic material was filtered off, and the ether–benzene layer washed with 5% sodium carbonate solution and then water, and dried (Na_2SO_4). Removal of the solvent and recrystallisation of the residue from benzene gave 3 : 4-benzocinnoline (2·7 g., 92% yield) as pale yellow blades, m. p. 156°.

Reduction of 1 : 2-*Benzophenazine.*—Attempted reduction of 1 : 2-benzophenazine (Ullmann and Heisler, *Ber.*, 1909, **42**, 4263) with sodium and methyl alcohol, with sodium and *iso*amyl alcohol, with ammonium sulphide and sodium hydroxide in boiling aqueous alcohol, and with alkaline sodium sulphide, all gave unchanged material. It was, however, reduced catalytically, as follows. A solution of 1 : 2-benzophenazine (1·0 g.) in alcohol (150 c.c.) was hydrogenated over Raney nickel catalyst until the rate of hydrogenation became very slow. The solution was filtered from the catalyst, concentrated, and allowed to cool. The crystals which separated were orange-red, and were purified by passage (in benzene solution) through a column of alumina. A narrow, dark red band formed at the top of the column, and a broad pale yellow band moved rapidly through the column on elution with benzene. Concentration of the eluate gave 1′ : 2′ : 3′ : 4′-*tetrahydro*-1 : 2-*benzophenazine*, which on further crystallisation formed pale yellow needles, m. p. 125° (Found : C, 82·4; H, 5·7. $C_{16}H_{14}N_2$ requires C, 82·05; H, 6·0%). The dark red band was also eluted but gave only a small amount of a dark red oil on removal of the solvent.

The same tetrahydro-1 : 2-benzophenazine, m. p. 125°, was also obtained by reduction of 1 : 2-benzophenazine with hydrogen over palladised charcoal.

We are grateful to Mr. R. S. Pearce for the absorption spectra, and to Mr. R. T. Howard for the microanalyses. One of us (J. H. S.) has been the recipient of Rennie Scholarship, and we are also indebted to the State Research Fund for a maintenance grant (to B. T.).

JOHNSON CHEMICAL LABORATORIES, UNIVERSITY OF ADELAIDE. [*Received, May 15th*, 1951.]

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707. *Polynuclear Heterocyclic Systems. Part IV.* The Linear Pentacyclic Compounds.*

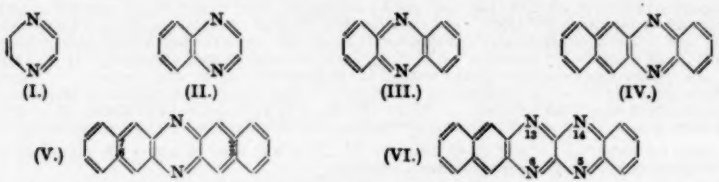
BY G. M. BADGER and R. PETTIT.

The linear heterocyclic compounds pyrazine, quinoxaline, phenazine, 2 : 3-benzophenazine, etc., have been compared with their carbocyclic analogues, and Dutt's claim (*J.*, 1926, 1179) to have prepared 5 : 7 : 12 : 14-tetra-azapentacene (VII) and 5 : 7 : 9 : 14 : 16 : 18-hexa-azaheptacene (VIII) is disputed. A dihydro-derivative of (VII) has been prepared by a number of methods, and has been given the structure (IX). On reductive acetylation it gave 5 : 7 : 12 : 14-tetra-acetyl-5 : 7 : 12 : 14-tetrahydro-5 : 7 : 12 : 14-tetra-azapentacene (XI). Mild oxidation failed to give the aromatic structure (VII), and more vigorous oxidation gave 5 : 7 : 12 : 14-tetra-azapentacene-6 : 13-quinone (XII), which was converted into 6 : 13-diacetoxy-5 : 7 : 12 : 14-tetra-acetyl-5 : 7 : 12 : 14-tetrahydro-5 : 7 : 12 : 14-tetra-azapentacene (XIII) on reductive acetylation. The quinonoid dihydro-compound (IX) seems to be more stable than the aromatic structure (VII).

IT is well known that in the series of linear benz-homologues of benzene, namely, benzene, naphthalene, anthracene, naphthacene, pentacene, etc., there is a very pronounced increase in the " reactivity " of the *meso*-positions as the number of rings increases. This is also correlated with the increased stability of the *meso*-dihydro-derivatives, with an increasing shift in the positions of the absorption bands towards the red, and with an increasing depth of the colours of the compounds themselves (Clar, " Aromatische Kohlenwasserstoffe," Springer-Verlag,

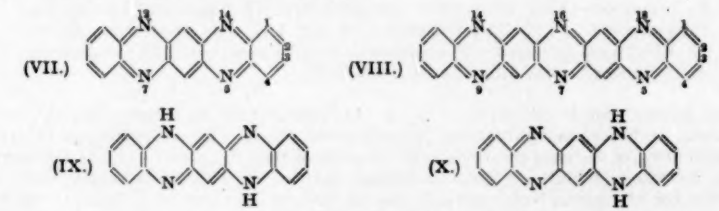
* Part III, preceding paper.

Berlin, 1941). It does not seem to have been noted previously, however, that similar relations in the reactivity of the *meso*-position and in the stability of the related dihydro-derivatives may be observed among the heterocyclic analogues of these compounds. The " reactivity " of the heterocyclic compounds, and the stability of the *meso*-dihydro-compounds increases progressively with the number of rings. For example, in the azine series, pyrazine (I) and quinoxaline (II) do not seem to give stable dihydro-derivatives. Phenazine (III) gives a dihydro-derivative which is only moderately stable, for it is oxidised in air to a molecular compound of phenazine and dihydrophenazine. This complex itself is oxidised very readily, even with mild oxidising agents such as ferric chloride. On the other hand, 2 : 3-benzophenazine (IV) gives a dihydro-compound with the greatest of ease and, although this is stable in air, it can be oxidised to the aromatic structure with dichromate (Hinsberg, *Annalen*, 1901, **319**, 257). 2 : 3-6 : 7-Dibenzophenazine (6 : 13-diazapentacene) (V) has never been prepared, for it cannot be obtained by oxidation of the dihydro-derivative, the latter being exceptionally stable (Hinsberg, *loc. cit.*). The dihydro-derivative of the aromatic compound 5 : 6 : 13 : 14-tetra-azapentacene (VI) is also exceptionally stable, and resisted attempts to oxidise it (Hinsberg, *loc. cit.*).



That the colour of the linear heterocyclic compounds should deepen as the number of rings increases follows from the similarities between the absorption spectra of the aromatic hydrocarbons and azahydrocarbons, as already discussed in Part I (*J.*, 1951, 3199). Thus pyridine, quinoline, and acridine are colourless, but 2 : 3-benzacridine, like the analogous hydrocarbon naphthacene, is orange-red. Similarly, pyrazine (I) and quinoxaline (II) are colourless, but phenazine (III), which begins to absorb at slightly longer wave-lengths than anthracene or acridine (see Part I, *loc. cit.*), is yellow. In the same way, 2 : 3-benzophenazine (IV) must absorb at slightly longer wave-lengths than naphthacene, for it is a red compound. The same relationship may be observed in other series of aromatic azahydrocarbons. The naphthacene analogue, 5 : 6 : 11 : 12-tetra-azanaphthacene, for example, is red-brown (Hinsberg, *loc. cit.*). There is no doubt, therefore, that all the azahydrocarbons should be of very nearly the same colour, often somewhat deeper, as their hydrocarbon analogues.

This evidence clearly invalidates Dutt's claim (*J.*, 1926, 1178) to have prepared 5 : 7 : 12 : 14-tetra-azapentacene (VII) and 5 : 7 : 9 : 14 : 16 : 18-hexa-azaheptacene (VIII). Dutt condensed 2 : 3-diaminophenazine with *o*-benzoquinone in concentrated sulphuric acid solution, and isolated a yellow crystalline solid, apparently having the correct composition (nitrogen analysis given). The compound isolated cannot have been a tetra-azapentacene, however, for the analogous aromatic hydrocarbon, pentacene, is deep blue (Clar, *loc. cit.*). Similarly, the compound isolated by Dutt by condensation of 2 : 3-diaminophenazine and 2 : 3-dihydroxy-phenazine in sulphuric acid cannot have been a hexa-azaheptacene. The compound isolated was described as forming microscopic yellow needles, but the analogous hydrocarbon, heptacene, would be deep green, almost black (Clar, *loc. cit.*).

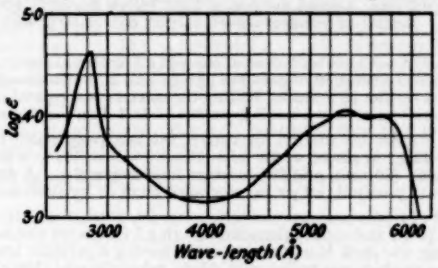


Numerous attempts have now been made to repeat Dutt's preparation of tetra-azapentacene (VII), but all have been unsuccessful. Only unchanged 2 : 3-diaminophenazine could be

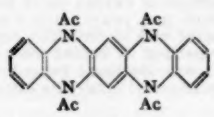
isolated from the reaction mixture. This is not surprising, for *o*-benzoquinone is extremely unstable and would not be expected to survive long in sulphuric acid. Attempts have also been made to carry out the condensation under other, usually milder, conditions, but no pure condensation product could be isolated. Attempts have also been made to use the more stable *o*-toluquinone, but these also failed to yield any product analogous to tetra-azapentacene. These experiments may be compared with those of Hinsberg (*loc. cit.*), who likewise failed to obtain other aromatic aza-pentacenes, and it seems likely that these substances must be too unstable to be prepared. Hinsberg found the dihydro-derivatives of his azapentacenes to be quite stable, and the same appears to hold with the present type of aza-compound. A dihydro-5 : 7 : 12 : 14-tetra-azapentacene has long been known under the name of " homofluorindine," and it is the parent substance of a group of coloured compounds known as " fluorindines." It was prepared by Fischer and Hepp (*Ber.*, 1890, **23**, 2791) by fusing together 2 : 3-diaminophenazine and *o*-phenylenediamine, but on p. **3214** we give an improved preparation, affording a purer product. It has also been obtained by heating *o*-phenylenediamine and its hydrochloride in the presence of air, and an additional method of preparation is described below. No conclusion seems to have been reached regarding the structure of this dihydro-compound, but in view of its very deep blue colour and its absorption spectrum (see figure), there can be no doubt that it has the asymmetrical " quinonoid " structure (IX), and is not the symmetrical dihydro-compound (X).

Catalytic reduction of the dihydro-compound (IX) gave a colourless solution (presumably of the tetrahydro-compound) but this was rapidly oxidised in air to give a deep blue solution

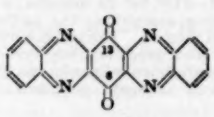
Absorption spectrum of 5 : 12-*dihydro*-5 : 7 : 12 : 14-*tetra-azapentacene in methanol.*



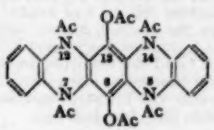
of the original dihydro-compound. On reductive acetylation, however, 5 : 7 : 12 : 14-tetra-acetyl-5 : 7 : 12 : 14-tetrahydro-5 : 7 : 12 : 14-tetra-azapentacene (XI) was obtained. This derivative is useful as, unlike the deep blue (IX), it has a melting point, and may therefore be used for purposes of identification. Many attempts to oxidise the dihydro-compound (IX) to the aromatic structure (VII) were made, but all proved unsuccessful. It seems certain, there-



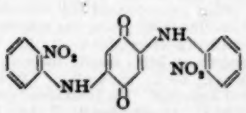
(XI.)



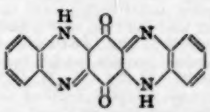
(XII.)



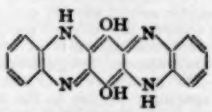
(XIII.)



(XIV.)



(XV.)



(XVI.)

fore, that the quinonoid system present in (IX) is more stable than the aromatic system (VII), and this is of some theoretical importance. Satisfactory conditions have, however, been found for the oxidation of the dihydro-compound (IX) to the quinone (XII), which has also been con-

verted into 6 : 13-diacetoxy-5 : 7 : 12 : 14-tetra-acetyl-5 : 7 : 12 : 14-tetrahydro-5 : 7 : 12 : 14-tetra-azapentacene (XIII) by being boiled with zinc dust and acetic anhydride.

According to Leicester (*Ber.*, 1890, **23**, 2794), 2 : 5-di-*o*-nitroanilinobenzoquinone (XIV) is reduced by alcoholic hydrogen sulphide in a sealed tube to a blue compound, which was given the structure (XV). The only evidence supporting this structure was the analysis, and it is significant that the calculated and the found value for hydrogen differed by as much as 1·6%. In any case the structure (XV) is impossible as it involves two tervalent carbon atoms. The structure (XVI), however, seems reasonable, and moreover, agrees with Leicester's analysis. Nevertheless, the formation of such a compound seemed unlikely, especially in view of the synthesis of "azophenine" from *p*-benzoquinone and aniline; the synthesis has therefore been reinvestigated. The reduction of (XIV) has now been carried out, not only by Leicester's method, but also with sodium sulphide and acetic acid, with sodium sulphide and ammonium chloride, with hydrogen and Raney nickel, and with Raney nickel alloy and sodium hydroxide solution. In every case the dihydrotetra-azapentacene (IX) was obtained and identified by reductive acetylation to the tetra-acetyl-derivative (XI). It seems certain, therefore, that the reaction proceeds by reduction of nitro- to amino-groups, followed by elimination of water with the quinone (or quinol) groups.

Experimental.

Attempts to prepare 5 : 7 : 12 : 14-*Tetra-azapentacene.*—The following experiments are typical: (i) *o*-Benzoquinone (0·54 g.) was added, in small portions with stirring, to a solution of 2 : 3-diaminophenazine (1·05 g.) in concentrated sulphuric acid (40 c.c.). After 1 hour, the mixture was poured into water, and the precipitated dark brown powder (0·7 g.) was collected. Attempts to obtain a pure substance by recrystallisation from nitrobenzene (cf. Dutt, *loc. cit.*) and other solvents were unavailing. After sublimation at 280°/0·2 mm., a small amount of light yellow material, identified as 2 : 3-diaminophenazine, was obtained. Similar experiments were carried out in 80% and in 50% sulphuric acid, and in acetic acid.

(ii) A suspension of finely powdered lead tetra-acetate (2 g.) in glacial acetic acid (20 c.c.) was slowly added with vigorous stirring to a solution of catechol (0·5 g.) and 2 : 3-diaminophenazine (1 g.) in glacial acetic acid (30 c.c.). After a further 90 minutes' stirring the mixture was poured into water. Purification of the resulting black material gave only a small quantity of 2 : 3-diaminophenazine.

(iii) In an attempt to prepare the methyl derivative, the relatively stable *o*-toluquinone was used. 2 : 3-Diaminophenazine (0·42 g.) in glacial acetic acid (25 c.c.) was added to a solution of *o*-toluquinone (0·25 g.) in glacial acetic acid (10 c.c.), and the mixture kept overnight. A dark red-brown solid was obtained, but all attempts to purify it, either by recrystallisaion or by sublimation, failed.

5 : 12-*Dihydro*-5 : 7 : 12 : 14-*tetra-azapentacene* (IX.).—(i) (cf. Fischer and Hepp, *loc. cit.*) A mixture of 2 : 3-diaminophenazine (8 g.) and *o*-phenylenediamine (6 g.) in benzyl alcohol (60 c.c.) was refluxed for 14 hours. After cooling, the dark blue-green crystals, having a metallic lustre, were collected, and washed with ethanol. The product was boiled with dilute sulphuric acid (100 c.c.), then with alcoholic ammonia (200 c.c.), and filtered off and dried. 5 : 12-Dihydro-5 : 7 : 12 : 14-tetra-azapentacene was obtained as a deep blue-purple powder (7·8 g.). It was only very sparingly soluble in all the usual organic solvents, giving deep blue solutions with a red fluorescence. It also dissolved in concentrated sulphuric acid to give a blue solution with a red fluorescence. For analysis and spectrographic examination, a sample was sublimed at 280—290°/0·1 mm. (Found: C, 75·8; H, 4·1. Calc. for $C_{18}H_{12}N_4$: C, 76·0; H, 4·2%).

(ii) A mixture of *o*-phenylenediamine (4·3 g.) and *o*-phenylenediamine dihydrochloride (3·5 g.) in naphthalene (60 g.) was heated at 210—215° for 20 minutes, a slow stream of oxygen being passed through the molten mass. After cooling somewhat, the molten mixture was poured into ethanol (200 c.c.), and the suspension boiled and filtered. The residue was extracted with more boiling ethanol (200 c.c.) and the resulting small shiny dark green crystals were further purified by boiling them with alcoholic ammonia (50 c.c.). The dihydrotetra-azapentacene (0·75 g.) was identified by reductive acetylation and direct comparison with an authentic specimen of the tetra-acetyltetrahydrotetra-azapentacene (XI) (see below).

5 : 7 : 12 : 14-*Tetra-acetyl*-5 : 7 : 12 : 14-*tetrahydro*-5 : 7 : 12 : 14-*tetra-azapentacene* (XI).—A mixture of 5 : 12-dihydro-5 : 7 : 12 : 14-tetra-azapentacene (0·5 g.), zinc dust (0·5 g.), sodium acetate (0·2 g.), and acetic anhydride (20 c.c.) was boiled under reflux until the blue colour disappeared (45 minutes). After cooling, the product was collected, and the zinc, which had coagulated into one piece, was removed. After recrystallisation from nitrobenzene, 5 : 7 : 12 : 14-*tetra-acetyl*-5 : 7 : 12 : 14-*tetrahydro*-5 : 7 : 12 : 14-*tetra-azapentacene* (0·4 g.) formed colourless needles, which began to darken at 340°, finally melting at 375—376° (sealed tube) (Found: C, 68·25; H, 5·2. $C_{26}H_{22}O_4N_4$ requires C, 68·7; H, 4·9%). It was very sparingly soluble in the usual organic solvents, such as alcohol and benzene. On treatment with mineral acids it was very readily hydrolysed (and oxidised in the air) to 5 : 12-dihydro-5 : 7 : 12 : 14-tetra-azapentacene.

Dihydrotetra-azapentacene (IX) *by Reduction of* 2 : 5-*Di-o-nitroanilinobenzoquinone.*—(i) A mixture of nitroanilinobenzoquinone (0·5 g.) and alcoholic ammonium sulphide (12 c.c.; containing *ca.* 5 g. of ammonium sulphide) was heated in a sealed tube at 100° for 2 hours. After it had cooled, no colourless crystals could be seen in the tube as stated by Leicester (*loc. cit.*). The product (0·45 g.) was obtained

as shiny, very dark-green, metallic-looking crystals, and was identified as dihydrotetra-azapentacene. Reductive acetylation in the usual way gave tetra-acetyltetrahydrotetra-azapentacene (XI) as colourless needles, m. p. 374—376°, alone or mixed with an authentic specimen.

(ii) A mixture of the nitroanilinoquinone (2·0 g.), sodium sulphide hydrate (15 g.), and ammonium chloride (2·5 g.) in water (400 c.c.) was boiled under reflux for 3 hours. Further quantities of sodium sulphide (7·5 g.) and ammonium chloride (1·7 g.) were then added, and the refluxing continued for a further 2 hours. The product (1·2 g.) obtained by filtration was again identified as dihydrotetra-azapentacene. The same compound was also obtained in less satisfactory yield by reduction and cyclisation with sodium sulphide and acetic acid, with hydrogen and Raney nickel catalyst at 100—120° and 1000 lb./in.², and by addition of Raney nickel alloy in small portions to a solution of the nitroanilinoquinone in aqueous sodium hydroxide, at 90°.

Oxidation of 5 : 12-*Dihydro*-5 : 7 : 12 : 14-*tetra-azapentacene*.—Attempts to oxidise dihydrotetra-azapentacene to tetra-azapentacene with hydrogen peroxide in acetic acid, either at room temperature or under reflux, were unsuccessful. In these experiments, and in runs with other oxidising agents, mixtures were obtained, from which no pure product could be isolated. Under more vigorous conditions, however, the quinone was obtained. 5 : 12-Dihydro-5 : 7 : 12 : 14-tetra-azapentacene (0·5 g.) was dissolved in concentrated sulphuric acid (180 c.c.), and the resulting deep blue solution added dropwise to a well-stirred solution of potassium dichromate (8 g.) in water (250 c.c.) at room temperature. After the addition was completed, the fine microcrystalline yellow product (0·44 g.) was collected, washed with water, and dried. 5 : 7 : 12 : 14-*Tetra-azapentacene*-6 : 13-*quinone* (XII) was very sparingly soluble in alcohol, benzene, and chloroform, but slightly more soluble in pyridine. After recrystallisation from nitrobenzene, it formed bright golden-yellow plates, m. p. above 400°, and for analysis was further purified by sublimation at 320°/0·1 mm. (Found: C, 69·3; H, 2·6. $C_{18}H_8O_2N_4$ requires C, 69·2; H, 2·6%).

6 : 13-*Diacetoxy*-5 : 7 : 12 : 14-*tetra-acetyl*-5 : 7 : 12 : 14-*tetrahydro*-5 : 7 : 12 : 14-*tetra-azapentacene*.—A mixture of the above quinone (1·0 g.), zinc dust (1·0 g.), anhydrous sodium acetate (0·4 g.), and acetic anhydride (30 c.c.) was boiled under reflux. The solution immediately became greenish-blue, slowly changed to red, and finally, after 1 hour, became colourless. After cooling, the mixture was poured into water, and the suspension stirred for 1 hour to complete hydrolysis of the excess of acetic anhydride. The product was decanted from the excess of zinc dust, washed with water, and dried. The 6 : 13-*diacetoxy*-5 : 7 : 12 : 14-*tetra-acetyl*-5 : 7 : 12 : 14-*tetrahydro*-5 : 7 : 12 : 14-*tetra-azapentacene* (1·3 g.) obtained was practically insoluble in ethanol, chloroform, and benzene. After recrystallisation from nitrobenzene, it formed small colourless plates, which decomposed gradually above 350° in a sealed capillary tube (Found: C, 63·5; H, 5·0. $C_{30}H_{24}O_8N_4$ requires C, 63·2; H, 4·6%).

Microanalyses were carried out by the C.S.I.R.O. Microanalytical Laboratory, Melbourne. We are grateful to Mr. R. S. Pearce for the absorption spectrum.

JOHNSON CHEMICAL LABORATORIES, UNIVERSITY OF ADELAIDE. [*Received, May 15th*, 1951.]

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708. *Aromatic Hydrocarbons. Part LXI.* Pentaphene.*

By E. CLAR and D. G. STEWART.

Pentaphene (IX) has been synthesised, the dispiran (V) being used as an intermediate.

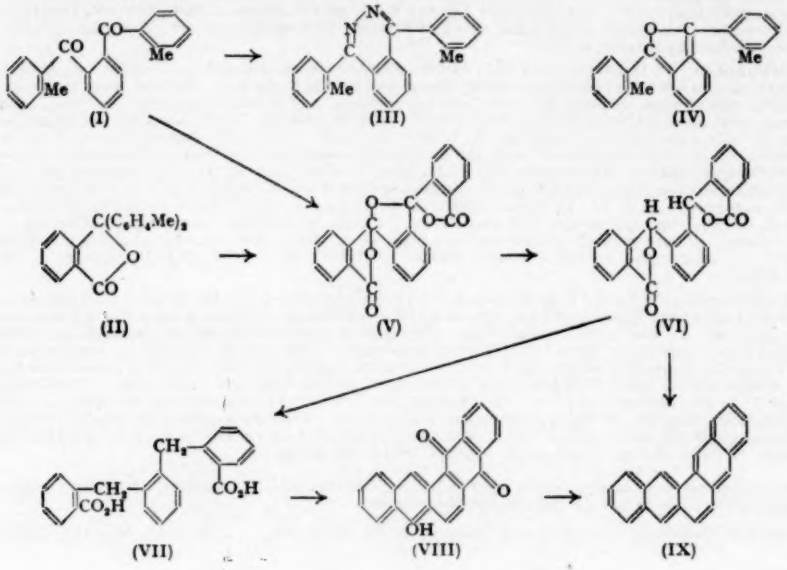
IT has been claimed (Weisz and Korczyn, *Monatsh.*, 1924, **45**, 207; Weisz and Müller, *ibid.*, 1934, **65**, 481) that the two products of different melting point obtained from the reaction of *o*-tolylmagnesium bromide with phthalic anhydride have the phthalide constitution. The higher-melting (m. p. 176°) has now been synthesised by oxidation of tri-*o*-tolylcarbinol with dilute nitric acid, and is without doubt di-*o*-tolylphthalide (II). We have found, however, that the second product (m. p. 128—131°) is a mixture of the phthalide (II) and 1 : 2-di-*o*-toluoylbenzene (I). The tendency for the formation of the latter is so pronounced that even the reaction of *as*-phthaloyl chloride with *o*-tolylmagnesium bromide yields mostly the diketone (I) and only a little phthalide (II). Mono-*o*-tolylphthalide and 2-*o*-toluoylbenzoic acid were obtained as by-products, both of which gave benzophenone-2 : 2′-dicarboxylic anhydride on oxidation with alkaline potassium permanganate solution.

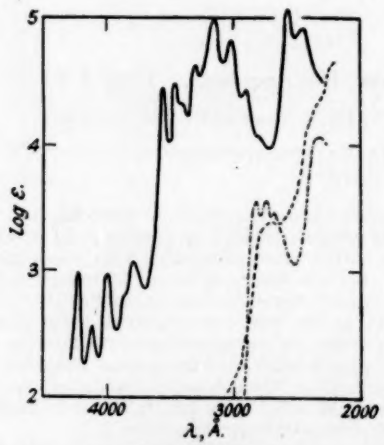
The structure of (I) was proved by its condensation with hydrazine hydrate to give 1 : 4-di-*o*-tolylphthalazine (III). The reaction also served for isolation of the pure phthalide (II), as the azine remained in the alcoholic solution, while the phthalide crystallised out unchanged. A good qualitative test for the presence of the diketone (I) is reduction by zinc in acetic acid,

* Part LX, *Nature*, 1950, **166**, 1075.

which yields a yellow, blue-fluorescent solution of the *iso*benzofuran (IV). The interesting properties of the corresponding diphenyl compound were studied in detail by Guyot and Catel (*Compt. rend.*, 1905, **140**, 1349; *Bull. Soc. chim.*, 1906, **35**, 1124).

The pure diketone (I) melted at 146°; when mixed with an equal amount of the pure phthalide (II), it melted at 125—128°, which corresponds with the m. p. of Weisz and Korczyn's second alleged phthalide (*loc. cit.*).





Absorption spectra.

———— *Pentaphene in alcohol. Band maxima (in* Å) : 4235, 4120, 3990, 3790; 3560, 3450, 3290; 3145, 3020, 2895; 2575, 2450.

— · — · — o-*Di*-(3-*phthalidyl*)*benzene* (VI) *in alcohol. Band maxima (in* Å) : 2820, 2750, 2680; 2350.

- - - - - - - *Disodium salt of* 1 : 2-*di*-o-*carboxybenzylbenzene* (VII) *in water. Band maximum at* 2700 Å.

The diketone (I) was oxidised with dilute nitric acid under pressure, or alternatively in two stages, *viz.*, first with dilute nitric acid solution and then with alkaline potassium permanganate solution, to a dicarboxylic acid which crystallised from acetic acid as the dispiran (V). Similar oxidations of the phthalide (II) gave, owing to rearrangement, good yields of (V) with only a minor proportion of what is believed to be the unrearranged dicarboxylic acid derived from (II). As the latter was soluble in acetic acid or acetic anhydride, pure (V) was readily obtained by oxidation, as described above, of the mixture of (I) and (II) resulting from the Grignard reaction of phthalic anhydride with *o*-tolylmagnesium bromide and crystallisation from acetic acid.

It is noteworthy that the melting point of the compound (V) corresponds exactly with that of Weisz and Korczyn's alleged triphenylmethane-2 : 2′ : 2″-tricarboxylic acid (*loc. cit.*) and that the melting points of their methyl esters are also very similar.

The dispiran (V) was reduced quantitatively by zinc dust and dilute sodium hydroxide solution to the double phthalide (VI). Further reduction with hydriodic acid and red phosphorus gave the acid (VII) and also, owing to a simultaneous ring closure, pentaphene (IX). Ring closure of the acid (VII) with concentrated sulphuric acid gave the reddish-brown 8-hydroxypentaphene-5 : 14-quinone (VIII). When (VII) and (VIII) were submitted to zinc-dust fusion (Clar, *Ber.*, 1939, **72**, 1645) pentaphene (IX) was obtained. This preparation of pentaphene is simpler and more efficient than the earlier synthesis (Clar and John, *Ber.*, 1931, **64**, 981) which involves a laborious separation from the accompanying dihydropentacene.

The absorption spectrum (see figure) shows the purity of the pentaphene obtained. The absorption spectra of (VI) and (VII), which are of the simple benzene type, are also reproduced.

Experimental.

(All m. p.s are uncorrected and were taken in evacuated capillaries. Microanalyses are by Miss R. H. Kennaway.)

Reaction of Phthalic Anhydride with o-Tolylmagnesium Bromide.—Procedure was as described by Weisz and Korczyn (*loc. cit.*). An 80% yield of colourless crystals of (I) and (II) (m. p. 126—130°) was obtained.

Tri-o-tolylcarbinol.—*o*-Toluoyl chloride (65 g.) in anhydrous ether (50 c.c.) was slowly added to a solution of *o*-tolyl-lithium prepared from *o*-bromotoluene (207·5 g.) and " atomised " lithium (16·8 g.). After decomposition of the mixture with dilute hydrochloric acid, the ethereal layer was concentrated and diluted with light petroleum. The crystals (110 g.) were recrystallised from light petroleum and yielded colourless needles (m. p. 105°) and a by-product (8%) (m. p. 240—242°). The carbinol dissolved readily in concentrated sulphuric acid to give an orange solution. The properties of the carbinol agree with those described for a sample prepared by a different method (cf. Faber and Nauta, *Rec. Trav. chim.*, 1942, **61**, 469; Theilacker and Ewald, *Naturwiss.*, 1943, **31**, 302).

Di-o-tolylphthalide (II).—The carbinol (75 g.) mixed with nitrobenzene (30 c.c.) was boiled in 20% nitric acid (1500 c.c.) for 16 hours, fumes of nitrogen oxides being evolved. After distillation of the nitrobenzene, the light yellow solid obtained was extracted thoroughly with boiling dilute sodium hydroxide solution to remove over-oxidised material, washed well with water, and crystallised first from glacial acetic acid and then from ethanol, to give colourless plates (68 g.), m. p. 174° (Found : C, 83·7; H, 5·5. Calc. for $C_{22}H_{18}O_3$: C, 84·0; H, 5·8%). The phthalide gave an orange-red solution in concentrated sulphuric acid which changed first to orange, then to pale yellow. The m. p. compares with that of the higher-melting phthalide (m. p. 176°) reported by Weisz and Müller (*loc. cit.*).

Reaction of as-Phthaloyl Chloride with o-Tolylmagnesium Bromide.—*o*-Tolylmagnesium bromide, prepared from *o*-bromotoluene (140 g.) and magnesium (21 g.) in ether (350 c.c.), was added to *as*-phthaloyl chloride (70 g.) in benzene (300 c.c.). After the usual decomposition and separation of the aqueous layer, concentration of the organic layer gave colourless crystals (12·5 g.) of *o-tolylphthalide* (m. p. 262°) (Found : C, 79·6; H, 5·4. $C_{15}H_{12}O_2$ requires C, 80·3; H, 5·4%), which gave a colourless solution in concentrated sulphuric acid. The mother-liquors, after extraction with dilute sodium hydroxide solution (10%) to remove 2-*o*-toluoylbenzoic acid (20 g.), were steam-distilled, and the resulting solid was crystallised from acetic acid to give colourless crystals, m. p. 125—129° (73 g.). Further crystallisation, first from benzene and then from ethanol, gave the pure 1 : 2-*di-o-toluoylbenzene* (I), m. p. 146° (76% of mixture) (Found : C, 83·8; H, 5·5. $C_{22}H_{18}O_2$ requires C, 84·0; H, 5·8%), which gave a pale yellow solution in concentrated sulphuric acid. Hot acetic acid and zinc dust yield a yellow solution of (IV) which shows a strong blue fluorescence. Both by-products, *o*-tolylphthalide and 2-*o*-toluoylbenzoic acid, on oxidation with alkaline potassium permanganate solution and recrystallisation from concentrated nitric acid gave colourless crystals, m. p. 212°, which gave a mixed m. p. of 212° with an authentic sample of benzophenone-2 : 2′-dicarboxylic acid anhydride.

1 : 4-*Di-o-tolylphthalazine* (III).—The mixture (m. p. 125—129°) (1 g.) was dissolved in ethanol (15 c.c.), hydrazine hydrate (100%) (0·18 c.c.) added, and the solution refluxed for 1 hour. Concentration yielded colourless plates, m. p. 174° (0·2 g.), which gave a mixed m. p. of 174° with an authentic sample of di-*o*-tolylphthalide (II). Dilution of the mother-liquors with water gave a white precipitate (0·75 g.) which, on crystallisation from ethanol, yielded colourless crystals, m. p. 162—163°, of 1 : 4-*di-o-tolylphthalazine* (III) (Found : N, 9·0. $C_{22}H_{18}N_2$ requires N, 9·0%). This gave a colourless solution in concentrated sulphuric acid.

Oxidation of 1 : 2-*Di*-o-*toluoylbenzene* (I) *and Di*-o-*tolylphthalide* (II).—(a) *With dilute nitric acid solution at* 210°. The diketone (I) (1 g.) was heated under pressure with 20% nitric acid at 210° for 10 hours. The solid obtained crystallised from acetic anhydride, to give colourless needles of (V), m. p. 302—303° (yield, theoretical).

(b) The phthalide (II) gave in the same way 60% of (V), m. p. 302—303°, and from the mother-liquor 35% of syrupy unrearranged dicarboxylic acid derived from (II); it did not crystallise and gave on heating with concentrated sulphuric acid and copper powder the blue condensation product described by Weiz and Korczyn (*loc. cit.*).

(c) *With dilute nitric acid solution, followed by alkaline potassium permanganate solution.* The diketone (I) (15 g.), mixed with nitrobenzene (6 c.c.), was boiled for 48 hours with 20% nitric acid (250 c.c.). After distillation of the nitrobenzene, the solid obtained was dissolved in dilute sodium hydroxide solution, and powdered potassium permanganate added till its colour persisted for 15 minutes. The filtrate was acidified and the precipitate crystallised from acetic anhydride (15 g.; m. p. 302—303°).

(d) A similar treatment of (II) yielded 75% of (V), m. p. 302—303°, and 20% of unrearranged dicarboxylic acid.

Oxidation of Mixture of (I) *and* (II).—Both methods of oxidation described above were applied to the mixture (m. p. 125—129°) of (I) and (II). Colourless needles, m. p. 302—303°, were obtained in both cases after crystallisation from acetic acid and acetic anhydride, the yields being 87% and 82%, respectively. The products (m. p. 302—303°) from the above oxidations, all proved to be *dihydroisobenzofuran*-1 : 3-*bis*spiro-(3-*phthalide*) (V), which sublimed in long colourless needles (Found: C, 74·2, 74·3; H, 3·5, 3·2. $C_{32}H_{18}O_6$ requires C, 74·2; H, 3·4%). The dispiran dissolved slowly in concentrated sulphuric acid to give a colourless solution which on being heated changed to dark green. 1 : 3-*Di*-(o-*carbomethoxyphenyl*)-1 : 3-*dihydroisobenzofuran*, prepared by refluxing (V) in methanol saturated with dry hydrogen chloride, crystallised from benzene in colourless needles or rods, m. p. 160° (Found: C, 71·6; H, 4·4. $C_{34}H_{18}O_6$ requires C, 71·6; H, 4·5%), which gave a colourless solution in concentrated sulphuric acid.

o-*Di*-(3-*phthalidyl*)*benzene* (VI).—The dispiran (V) was dissolved in boiling sodium hydroxide solution (15%) (200 c.c.), and zinc dust (20 g.) added during 2 hours. The initial yellow colour changed to a deep red, which persisted for 10 minutes. After 3 hours, the hot solution was filtered directly into concentrated hydrochloric acid, and the white precipitate crystallised from acetic acid. Colourless needles, m. p. 211—212°, of the *dilactone* (VI) (Found: C, 77·1; H, 4·3. $C_{32}H_{14}O_4$ requires C, 77·2; H, 4·1%) were obtained, which gave a colourless solution in concentrated sulphuric acid. The yield was theoretical.

1 : 2-*Di*-(o-*carboxybenzyl*)*benzene* (VII).—The dilactone (VI) (13 g.), red phosphorus (6 g.), and hydriodic acid (55%) (60 c.c.) were covered with xylene (60 c.c.), and after being refluxed for 36 hours, the mixture was filtered. The solid obtained was extracted with xylene and then with hot sodium hydroxide solution. The aqueous layer from the filtrate was extracted with xylene, and the combined xylene fractions then extracted with hot sodium hydroxide solution. The alkaline solutions obtained were acidified hot with concentrated hydrochloric acid, and the precipitate crystallised from acetic acid, to give colourless needles (10 g., 76%), m. p. 242—243°, of the *acid* (VII) (Found: C, 76·2; H, 5·2. $C_{32}H_{18}O_4$ requires C, 76·3; H, 5·2%).

8-*Hydroxypentaphene*-5 : 14-*quinone* (VIII).—The acid (VII) (3 g.) was dissolved in concentrated sulphuric acid (30 c.c.), and heated to 120° for 10 minutes. The initial pale yellow colour changed to reddish-brown and then to dark green. The cold solution was poured into water, and the reddish-brown precipitate obtained was recrystallised from nitrobenzene and sublimed in a vacuum. Dark red needles (2·6 g.), m. p. 349—351°, of 8-*hydroxypentaphene*-5 : 14-*quinone* (VIII) (Found: C, 80·9; H, 3·5. $C_{32}H_{16}O_3$ requires C, 81·5; H, 3·7%) were obtained which gave with alkaline sodium dithionite (hydrosulphite) solution a reddish-brown vat which lightens on storage.

Pentaphene (IX).—(a) *From the dilactone* (VI). In the preparation of the acid (VII), the xylene fractions, after extraction with dilute sodium hydroxide solution, were concentrated, and pale yellow needles (2 g.) crystallised, m. p. 255—257° alone or mixed with an authentic sample of pentaphene (Found: C, 94·3; H, 5·4. Calc. for $C_{32}H_{14}$: C, 94·9; H, 5·1%).

(b) *From* (VII) *or* (VIII) *by the zinc-dust melt.* The compound (VII) or (VIII) (1 part) was finely ground with zinc dust (1·2 parts) and sodium chloride (1·2 parts), and moist zinc chloride (7 parts) added. The temperature was raised with constant stirring to 300° during 15 minutes. The cold melt was decomposed with dilute acetic acid; the resulting solid was filtered off, dried, and sublimed in a vacuum. Crystallisation of the sublimate from xylene gave yellow needles, m. p. 255—256°, unchanged on admixture with pentaphene. The pentaphene was further purified by chromatography (alumina), benzene being used as eluant. The clear yellow, blue-fluorescent eluate gave on concentration pale yellow plates (m. p. 256—257°) which were insoluble in concentrated sulphuric acid.

UNIVERSITY OF GLASGOW.

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709. *Partial Asymmetric Synthesis with Keto-esters. Part I.*

By Joan A. Reid and E. E. Turner.

The interaction of phenylmagnesium bromide with (−)-menthyl lævulate and (−)-menthyl γ-acetyl-*n*-butyrate is accompanied by partial asymmetric synthesis.

Numerous partial asymmetric syntheses were achieved by McKenzie and his co-workers (*J.*, 1904, **85**, 1249 and later papers; for bibliography see Ritchie, *Adv. Enzymology*, 1947, **7**, 65) by the interaction of Grignard reagents and the (−)-menthyl (or bornyl) esters of α-keto-acids, followed by removal by hydrolysis of the " fixed centre of asymmetry " initially present:

$$R{\cdot}CO{\cdot}CO_2R^* \xrightarrow{R'{\cdot}MgX} R{\cdot}CR'(O{\cdot}MgX){\cdot}CO_2R^* \longrightarrow R{\cdot}CR'(OH){\cdot}CO_2R^* \longrightarrow R{\cdot}CR'(OH){\cdot}CO_2H$$

For example, interaction of (−)-menthyl pyruvate and phenylmagnesium halide led to atrolactic acid containing a preponderance of the (+)- over the (−)-form. A much less conclusive result was observed in the reaction between phenylmagnesium bromide and (−)-menthyl lævulate.

For reasons given in Part III (*J.*, 1951, 3227), we have examined, in as quantitative a manner as appeared to us to be possible, the extent of partial asymmetric synthesis in the interaction of phenylmagnesium bromide with a series of (−)-menthyl esters, $CH_3{\cdot}CO{\cdot}[CH_2]_x{\cdot}CO_2{\cdot}C_{10}H_{19}$, where x is 2, 3, 4, and 8, McKenzie's experiments with (−)-menthyl pyruvate ($x = 0$) being repeated in order to obtain figures which would serve as a basis for comparison with those we recorded with other esters. We describe the preparation of (−)-menthyl γ-acetyl-*n*-butyrate, δ-acetyl-*n*-valerate, and ω-acetylpelargonate.

In order to secure reproducibility of result, we first worked out conditions for preparing ethereal phenylmagnesium bromide of known concentration. An excess of magnesium was initially used and the reagent filtered in a closed apparatus in an atmosphere of dry nitrogen.

The desired reaction of the Grignard reagent with the keto-group can be succeeded, if the reagent is present in excess, by reaction with the carbomenthoxy-group, glycols being formed. In order to reduce this secondary reaction to a minimum, the Grignard reagent was added to a stirred or shaken ethereal solution of the keto-ester. As complete and quantitative an analysis as possible was made of the reaction products in every experiment. The (−)-menthyl x-hydroxy-x-phenylalkanecarboxylates were hydrolysed and optical examination was made of either the free hydroxy-acids or their lactones, if such were obtainable.

Interaction of (−)-menthyl pyruvate with 1·25 molecular proportions of phenylmagnesium bromide led finally to a 50% yield of atrolactic acid having $[\alpha]_D^{20}$ +7·8° (in water), a figure in fair agreement with that of McKenzie (*J.*, 1906, **89**, 365), who found $[\alpha]_D^{16}$ +5·4°. From data given by McKenzie and Clough (*J.*, 1910, **117**, 1016) it can be calculated that our product contained 18% of (+)- and 82% of (±)-atrolactic acid.

McKenzie (*J.*, 1906, **89**, 365) treated (−)-menthyl lævulate with phenylmagnesium bromide but obtained strongly coloured products which could not be satisfactorily examined for optical rotation. The interaction of (−)-menthyl lævulate with 1·25 molecular proportions of phenylmagnesium bromide has now been studied in some detail. Preliminary experiments showed that partial asymmetric synthesis did occur, (+)-γ-hydroxy-γ-phenylvaleric acid being formed in slight excess over the (−)-form. The specific rotation of the partially active acid was low, but the corresponding lactone, the formation of which was accompanied by a reversal in sign of rotation and no detectable racemisation, had a relatively high specific rotation. In studying the effect of conditions of reaction on yield and degree of asymmetric synthesis, the lactone was therefore prepared in all cases. The yield of lactone was found to decrease and the degree of asymmetric synthesis to increase with the time taken to mix the ester and Grignard reagent. Stirring of the reaction mixture for a considerable period after mixing also increased the extent of asymmetric synthesis. Thus, while the yield of lactone varied with change of conditions from about 60% to 40%, the specific rotation (in alcohol) varied from $[\alpha]_{5780}^{25}$ −3·0° to −7·0°. Experiments carried out using 2·25 and 4·0 molecular proportions of phenylmagnesium bromide gave γ-phenyl-γ-valerolactone in 26% and 12% yield respectively, and specific rotation $[\alpha]_{5780}$ −2·2° (c, 4·55) and $[\alpha]_{5780}$ −3·1° (c, 1·625), respectively.

The crude hydroxyphenylvaleric acid often contained a small quantity of an unsaturated acid, doubtless 4-phenylpent-3-enoic acid.* This was readily separable from the lactone. Since

* Geneva nomenclature ($CO_2H = 1$).

the lactone obtained when addition was over a very short time contained a negligible amount of unsaturated acid, the conditions used for the decomposition and subsequent working-up of the Grignard reaction mixture must have been satisfactory. Kloetzel (*J. Amer. Chem. Soc.*, 1940, **62**, 1708) obtained 4-phenylpent-3-enoic acid as the main product of the interaction of methyl β-benzoylpropionate and methylmagnesium iodide, and a similar result had been recorded by Mayer and Stamm (*Ber.*, 1923, **56**, 1424), using the ethyl ester.

Racemic γ-hydroxy-γ-phenylvaleric acid, synthesised from ethyl lævulate and phenylmagnesium bromide, forms a well-defined brucine salt, crystallisation of which from water permits of its optical resolution. The (+)-acid had $[\alpha]_{5461}$ +5·7° ± 0·2° in ethyl alcohol and gave a lactone with $[\alpha]_{5461}$ −61·9° ± 0·4° in ethyl alcohol. The enantiomeric lactone was obtained with $[\alpha]_{5461}$ +61·8° ± 0·5° in ethyl alcohol. The most active lactone derived by partial asymmetric synthesis contains, according to calculation, 12·5% of the (−)- and 87·5% of the (±)-form.

A curious example of partial "spontaneous" resolution was observed when a solution of the lactone having $[\alpha]_{5461}$ −7·0° in aqueous potassium hydroxide was fractionally acidified. The three successive crops had $[\alpha]_{5461}$ +4·95°, −2·54° and +0·03°, the lactones formed from the first 2 crops having $[\alpha]_{5461}$ −52·1° and +26·2° (rotations all in ethyl alcohol). Moreover, fractional acidification of a solution in alkali of the lactone of rotation +26·2° gave as a first crop an acid with $[\alpha]_{5461}$ −4·65° (lactone, +50·8°).

Interaction of (−)-menthyl γ-acetylbutyrate with 1·25 molecular proportions of phenylmagnesium bromide was accompanied by small but definite partial asymmetric synthesis. For optical examination the 5-hydroxy-5-phenylhexanoic acid produced was converted into its lactone; in one experiment this had $[\alpha]^{25}_{5461}$ −2·52° ± 0·15° in ethyl alcoholic solution. In these experiments slower mixing of the reactants decreased the extent of asymmetric synthesis.

Interaction of (−)-menthyl δ-acetylvalerate with 1·25 molecular proportions of phenylmagnesium bromide led to the ultimate isolation in high yield of 6-hydroxy-6-phenylheptanoic acid with α^{25}_{5461} +0·09° ($l = 2$) in ethyl alcohol. Partial asymmetric synthesis is thus demonstrated, but it appears to be slight.

Interaction of (−)-menthyl ω-acetylpelargonate and phenylmagnesium bromide, leading finally to 10-hydroxy-10-phenylundecanoic acid, was not accompanied by detectable partial asymmetric synthesis.

Experimental.

(−)-Menthyl pyruvate, prepared (yield 24%) by McKenzie's method (*J.*, 1905, **87**, 1373), had b. p. 132·5—133·5°/10 mm., n^{16}_{D} 1·4565, $[\alpha]^{16}_{D}$ −46·64°, $[\alpha]^{15}_{5780}$ −48·75°, and $[\alpha]^{15}_{5461}$ −55·74° ($l = 0{\cdot}5$).

(−)-Menthyl lævulate, prepared by McKenzie's method (*J.*, 1906, **89**, 365) (yield 71%), had b. p. 151°/2 mm., $n^{20{\cdot}5}_{D}$ 1·4573, $d^{20{\cdot}5}$ 0·9765, d^{25} 0·971, $[\alpha]^{20{\cdot}5}_{D}$ −61·14°, $[\alpha]^{20{\cdot}5}_{5780}$ −63·62°, $[\alpha]^{20{\cdot}5}_{5461}$ −72·01°, $[\alpha]^{25}_{5780}$ −63·49°, $[\alpha]^{25}_{5461}$ −71·84°. The semicarbazone, prismatic needles from ethyl alcohol, had m. p. 156—156·5°.

(−)-*Menthyl γ-Acetyl*-n-*butyrate* (5-*Ketohexanoate*).—(a) *γ-Acetyl*-n-*butyric acid*. A solution of *cyclo*hexane-1 : 3-dione (56 g.) in 4N-potassium hydroxide (500 c.c.) was boiled under reflux for 12 hours. The cooled solution was acidified with concentrated hydrochloric acid and extracted with ether in a continuous liquid–liquid extractor. When the ethereal extract was evaporated and the residual oil was stirred with a little water, 64 g. (87%) of acetylbutyric acid monohydrate were obtained (after crystallisation from water it had m. p. 37—37·5°). (The semicarbazone, prisms from water, had m. p. 172·5—173·5°.) By heating the monohydrate at 80°/5 mm., the anhydrous acid was obtained.

(b) (−)-*Menthyl γ-acetyl*-n-*butyrate*. The general method of McKenzie was used and the *ester* obtained in 45% yield, with b. p. 154·5—155·5°/3 mm., $n^{20{\cdot}5}_{D}$ 1·4588, d^{25} 0·973, $[\alpha]^{25}_{5780}$ −68·02°, $[\alpha]^{25}_{5461}$ −70·17° (Found: C, 72·2; H, 10·8. $C_{16}H_{28}O_3$ requires C, 71·6; H, 10·5%). The semicarbazone, plates from aqueous alcohol, had m. p. 125—125·5°.

(−)-*Menthyl δ-Acetyl*-n-*valerate* (6-*Ketoheptanoate*).—The method used for the preparation of δ-acetyl-*n*-valeric acid was essentially that used by McKennis and du Vigneaud (*J. Amer. Chem. Soc.*, 1946, **68**, 832). The (−)-*menthyl* ester, prepared from the acid by the general method of McKenzie, had b. p. 173—174°/3 mm., 186—187°/8 mm., $n^{20{\cdot}5}_{D}$ 1·4600, d^{25} 0·9605, $[\alpha]^{25}_{5780}$ −58·74°, $[\alpha]^{25}_{5461}$ −66·50°. In chloroform solution the ester had $[\alpha]^{19}_{5780}$ −63·2°, $[\alpha]^{19}_{5461}$ −72·2° (*c*, 1·5; $l = 2$) (Found: C, 72·4; H, 10·7. $C_{17}H_{30}O_3$ requires C, 72·3; H, 10·7%). The semicarbazone, plates from aqueous alcohol, had m. p. 105—106°.

(−)-*Menthyl ω-Acetylpelargonate* (10-*Ketoundecanoate*).—This was prepared by applying McKenzie's general method to the parent acid, which was obtained essentially as described by Myddleton and Barrett (*J. Amer. Chem. Soc.*, 1927, **49**, 2258). The *ester* had b. p. 209—210°/3—4 mm., d^{18} 0·944, d^{25} 0·939, $[\alpha]^{15}_{5780}$ −48·67°, $[\alpha]^{15}_{5461}$ −55·09°, $[\alpha]^{25}_{5780}$ −48·59°, $[\alpha]^{25}_{5461}$ −55·01° (Found: C, 74·4; H, 11·2. $C_{21}H_{38}O_3$ requires C, 74·5; H, 11·3%). The semicarbazone, plates from aqueous alcohol, had m. p. 100·5—101°.

Preparation of Ethereal Phenylmagnesium Bromide Solution.—Magnesium turnings (0·5 g.) were covered with ether, a little bromobenzene added, and the flask heated, with simultaneous replacement

of air in the apparatus by nitrogen, until reaction set in. A further 9·1 g. of magnesium were then introduced and covered with ether (total Mg, 0·396 g.-atom). An ethereal solution of bromobenzene (in all, 20·65 g., 0·132 g.-mol.) was then added at such a rate that gentle boiling occurred without external thermal adjustment. When all the bromobenzene had been added, the mixture was gently boiled for 30 minutes. After cooling, the ethereal solution was siphoned through glass wool into a separatory funnel. Ether was then introduced in order to wash out the flask and the glass wool.

In order to determine the approximate amount of diphenyl present in a Grignard reagent so prepared, the solution was poured on ice, and the mixture acidified with 5N-sulphuric acid. The layers were separated and the aqueous layer was extracted twice with ether. The combined ethereal extracts were washed thrice with water, thrice with 10% sodium carbonate solution, and then twice with water, dried (Na_2SO_4), and evaporated at about 20 mm. The residual diphenyl was weighed. The mean of a number of such determinations showed that the yield of phenylmagnesium bromide was 95%.

Partial Asymmetric Synthesis of Atrolactic Acid.—To an ethereal solution of (−)-menthyl pyruvate (4·52 g., 0·02 g.-mol.) was added, under nitrogen, an ethereal solution of phenylmagnesium bromide (0·025 g.-mol.) with ice-cooling and shaking during 30 minutes. The pale yellow solution was gently boiled for 2½ hours, cooled, and poured on 20 g. of ice. After acidification with 5N-sulphuric acid (25 c.c.), the two layers were separated and the aqueous layer was extracted 4 times with 20 c.c. of ether. The last extract was devoid of optical activity. The combined ethereal solutions were washed twice with 20 c.c. of water, once with 20 c.c. of 10% sodium carbonate solution, and then once with 20 c.c. of water. All the aqueous washings were optically inactive. Concentration of the dried (Na_2SO_4) ethereal solution gave a pale yellow oil (5·49 g.) which was boiled with 5N-potassium hydroxide (5 c.c.) and ethyl alcohol (20 c.c.) for 4 hours. The mixture formed two layers and therefore 5 c.c. of the alkali, 5 c.c. of ethyl alcohol, and 10 c.c. of water were added, the resulting homogeneous solution being boiled for 0·5 hour. Ethyl alcohol was then removed by distillation and the residue extracted 5 times with 20 c.c. of ether (extracts *A*). The last extract was optically inactive, showing that all menthol had been removed. The aqueous layer was acidified with 5N-sulphuric acid and extracted five times with 20 c.c. of ether. The aqueous layer was then optically inactive. The combined ethereal extracts were dried (Na_2SO_4) and evaporated. The residue was dried in a vacuum over calcium chloride and paraffin wax and gave 1·23 g. (50%) of atrolactic acid as a pale yellow solid which had $[\alpha]_D^{20}$ +7·8°, $[\alpha]_{5780}$ +8·2°, $[\alpha]_{5461}$ +9·5° (*c*, 6·15 in water), and $[\alpha]_D^{15}$ +6·7°, $[\alpha]_{5780}$ +6·8°, $[\alpha]_{5461}$ +8·1° (*c* 3·075 in absolute ethyl alcohol).

The ethereal extracts *A* were freed from solvent, menthol, and diphenyl by steam-distillation. The residual organic material (1-methyl-1 : 2 : 2-triphenylethylene glycol) was optically inactive.

*Partial Asymmetric Synthesis of γ-Hydroxy-γ-phenyl-*n*-valeric Acid and γ-Phenyl-γ-valerolactone.*—A solution of (−)-menthyl lævulate (20·34 g., 0·08 g.-mol.) in ether (80 c.c.) was cooled in ice, and an ethereal solution of phenylmagnesium bromide (0·10 g.-mol.) added during 30 minutes, with stirring which was thereafter continued for 1 hour. The mixture was kept overnight at 0° and then treated with ice (50 g.) and 5N-sulphuric acid (100 c.c.). The two layers were separated and the aqueous layer was extracted with 50 c.c. of ether 4 times. The combined ethereal solutions were thrice washed with 50 c.c. of water, 3 times with 20 c.c. of 10% sodium carbonate solution, and then thrice with 25 c.c. of water. The ethereal solution was dried (Na_2SO_4) and the residue (27·8 g.) boiled for 4 hours under reflux with 2·5N-potassium hydroxide (40 c.c.) and ethyl alcohol (80 c.c.). The alcohol was then distilled off and the residue freed from menthol and other neutral products by ether-extraction (9 × 50 c.c.). The alkaline aqueous layer was acidified with 5N-sulphuric acid and extracted with ether. The ethereal extract was washed with water and dried (Na_2SO_4). The ether was evaporated and the residue dissolved in benzene (75 c.c.). The benzene was distilled off and the operation twice repeated. The residue from the third benzene distillation was heated under reduced pressure for ½ hour at 100° and then kept in a vacuum over paraffin wax. Crude γ-phenyl-γ-valerolactone (6·68 g., 47%) remained, with $[\alpha]_{5780}$ −6·6°, $[\alpha]_{5461}$ −7·5° (*c*, 10·06 in ethyl alcohol). An ethereal solution of the crude lactone was extracted repeatedly with aqueous sodium carbonate, which removed much colour, and dried (Na_2SO_4). Removal of the solvent gave γ-phenyl-γ-valerolactone with $[\alpha]_{5780}$ −6·82°, $[\alpha]_{5461}$ −7·71° ± 0·05° (*c*, 10·11 in absolute ethyl alcohol) (Found : C, 74·5; H, 7·2. Calc. for $C_{11}H_{12}O_2$: C, 75·0; H, 6·9%). A portion of the lactone was distilled : it had b. p. 134—139°/7 mm., n_D^{15} 1·5282 (Found : C, 75·6; H, 6·8%). The rest was heated with aqueous sodium hydroxide, and the cooled solution acidified, whereupon a microcrystalline specimen of γ-hydroxy-γ-phenyl-*n*-valeric acid was obtained with $[\alpha]_{5780}$ +0·60°, $[\alpha]_{5461}$ +0·73° ± 0·1° (*c*, 3·97 in absolute ethyl alcohol) (Found : C, 67·8; H, 7·1. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·3%).

A large number of experiments was performed in order to detect any variation of degree of asymmetric synthesis with reaction conditions. Four examples may be quoted in which the time of addition of Grignard reagent to menthyl lævulate was varied :

Addition time (at 0°)	Lactone		
	Yield, %	$[\alpha]_{5780}^{25}$	*c*
1 min.	61	−3·0°	15·00
1 hour	44	−5·5	15·12
3 hours	46	−5·3	10·23
4 hours	39	−5·1	8·57

When the addition time was 30 minutes (0°) and the mixture was then stirred for an hour at 0° and kept overnight, the yield of lactone was 47—51% and $[\alpha]_{5780}$ −6·1° to −6·6° (*c*, 13—10) in different experiments.

Subsequent examination of the products termed " lactone " showed that, in all experiments except where addition was very rapid, these contained sensible quantities of free acid, probably 4-phenylpent-3-enoic acid. Removal of the free acid by means of aqueous sodium carbonate gave a pure lactone, without any great change in optical rotation.

Crude lactone			Lactone present, %	Purified lactone		
$[\alpha]_{5780}$	$[\alpha]_{5461}$	*c*		$[\alpha]_{5780}$	$[\alpha]_{5461}$	*c*
−5·3°	−6·0°	10·2	78	−5·7°	−6·7°	4·2
−6·6	−7·5	10·1	85	−6·8°	−7·7°	10·1

" Resolution " of lactone. A sample of lactone (2·0 g.) having $[\alpha]_{5461}$ −7·0° was dissolved in aqueous potassium hydroxide and the solution acidified to *ca.* pH 5 in 3 stages. Filtration at these stages gave acids *a*, *b*, and *c* as follows :

	g.	M. p.	$[\alpha]_{5461}$
Acid *a*	0·57	117·0—118·5°	+4·95°
Acid *b*	0·73	109·5—111·5	−2·54
Acid *c*	0·32	103·5—104·5	+0·03

Acid *a* gave a lactone with $[\alpha]_{5461}$ −52·1°, and acid *b* gave a lactone with $[\alpha]_{5461}$ +26·2°. The latter was dissolved in aqueous potassium hydroxide and acidified in stages. The acid first precipitated (0·27 g.) had m. p. 119·5—121° and $[\alpha]_{5461}$ −4·65° and gave a lactone with $[\alpha]_{5461}$ +50·8°. The whole series of observations was reproducible on four times this scale.

Preparation of (±)-γ-Hydroxy-γ-phenylvaleric Acid.—An ethereal solution of phenylmagnesium bromide (1·25 g.-mol.) was added to ethyl lævulate (144 g., 1·0 g.-mol.) in ether (1 l.), with ice-cooling and stirring, during 20 minutes. Stirring was continued for a further 10 minutes and the mixture kept overnight at 0°. Ice (500 g.) and 5N-sulphuric acid (1 l.) were added. The aqueous layer was extracted with ether, and the extract washed with water, aqueous sodium carbonate, and water. The ethereal layer was dried (Na_2SO_4) and the ether removed. The residual yellow oil (180 g.) was boiled under reflux with ethyl alcohol (1 l.) and 2·5N-potassium hydroxide (500 c.c.) for 5 hours. The cooled solution was extracted with ether, and the aqueous layer acidified and extracted with ether. The ethereal solution was washed with water and dried (Na_2SO_4). The ether was distilled off and the residue treated with benzene (250 c.c.). The solvent was removed and the operation twice repeated. The crude γ-phenyl-γ-valerolactone was dissolved in ether and washed six times with 10% aqueous sodium carbonate. The ether was removed and the residue dissolved in hot 2·5N-potassium hydroxide. The solution was warmed with charcoal, cooled, filtered, and then gradually acidified with 5N-sulphuric acid. γ-Hydroxy-γ-phenylvaleric acid was obtained as a microcrystalline solid (48 g., 27%). Crystallisation from benzene gave plates, m. p. 105·5—106° (Found: C, 68·2; H, 7·4. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·3%) (Trivedi and Nargund, *J. Univ. Bombay*, 1941, **10**, 102, give m. p. 106°. Johnson, Peterson, and Schneider, *J. Amer. Chem. Soc.*, 1947, **69**, 74, give 104—106°).

Optical Resolution of γ-Hydroxy-γ-phenylvaleric Acid.—The acid (9·7 g., 0·05 g.-mol.) was dissolved in warm water (200 c.c.), and brucine tetrahydrate (23 g., 0·05 g.-mol.) added. The solution was filtered and cooled. Rosettes of needles separated (13·47 g.) which had m. p. 105—110° (decomp.), $[\alpha]_{5780}$ −49·6°, $[\alpha]_{5461}$ −58·2° in chloroform (*c*, 0·998). After five crystallisations from water brucine (+)-γ-hydroxy-γ-phenylvalerate was obtained as sheaves of needles, m. p. 107—108° (decomp.), $[\alpha]_{5780}$ −64·9° ± 0·5°, $[\alpha]_{5461}$ −75·9° ± 0·5° (*c*, 0·995 in chloroform) (Found: C, 64·3; H, 7·3. $C_{34}H_{40}O_7N_2,2\frac{1}{2}H_2O$ requires C, 64·4; H, 7·1%). The salt was treated with excess of warm sodium hydroxide solution, and the brucine removed by three extractions with chloroform. The aqueous layer, freed from chloroform, was acidified with hydrochloric acid at 0° and extracted with ether. The ethereal extract was washed with water and dried (Na_2SO_4). The ether was removed and the residue dissolved in the minimum amount of hot 2·5N-potassium hydroxide. The solution was cooled to 0° and acidified. The γ-hydroxy-γ-phenylvaleric acid which separated had m. p. 122—122·5°, $[\alpha]_{5780}$ +4·8° ± 0·2°, $[\alpha]_{5461}$ +5·7° ± 0·2° (*c*, 2·544 in absolute ethyl alcohol). Dissolution in alkali and reprecipitation by acid did not affect the specific rotation, nor did crystallisation from benzene. The lactone, prepared by repeated distillation with benzene, as described previously, had $[\alpha]_{5780}$ −54·8° ± 0·4°, $[\alpha]_{5461}$ −61·9° ± 0·4° (*c*, 1·214 in absolute ethyl alcohol) (Found: C, 67·9; H, 7·3. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·3%).

The mother-liquor from which the 13·37 g. of brucine salt had separated was concentrated to 35 c.c., and filtered warm. When the solution was kept, a mixture of needles and plates separated with $[\alpha]_{5461}$ −27·5° (*c*, 1·002 in chloroform). It was freed from brucine and then dissolved afresh in water with the equivalent of brucine. From the solution plates separated, m. p. 95·5—98°, with $[\alpha]_{5461}$ +6·5° ± 0·1° (*c*, 5·062 in chloroform). Recrystallisation from water gave a salt with $[\alpha]_{5461}$ +5·8° ± 0·1° (*c*, 3·441 in chloroform). The brucine was removed and the free acid lactonised. The lactone had $[\alpha]_{5461}$ +61·8° ± 0·5° (*c*, 0·955 in ethyl alcohol) (Found: C, 67·3; H, 7·1. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·3%).

Partial Asymmetric Synthesis of 5-Phenyl-5-hexanolactone.—An ethereal solution of phenylmagnesium bromide (0·1 g.-mol.) was added during 30 minutes to an ice-cooled solution of (−)-menthyl γ-acetylbutyrate (21·47 g., 0·08 g.-mol.) in ether (80 c.c.), with stirring. A thick oil separated and stirring was continued at 0° for a further hour. After being kept for 12 hours at 0° the mixture was treated with ice (50 g.) and 5N-sulphuric acid (100 c.c.). The aqueous layer was extracted four times with 50 c.c. of ether. The combined ethereal extracts were washed with water (3 × 50 c.c.), with 10% aqueous sodium carbonate (3 × 25 c.c.), and with water (3 × 25 c.c.) and finally dried (Na_2SO_4).

After removal of the ether, a yellow oil (26·3 g.) was obtained. This was boiled under reflux with 2·5N-aqueous potassium hydroxide (40 c.c.) and ethyl alcohol (80 c.c.) for 4 hours. The alcohol was removed by distillation and the residue was extracted with ether (2 × 75 c.c. and 5 × 50 c.c.) to remove neutral products. The aqueous layer was acidified with 5N-sulphuric acid, and the δ-hydroxy-δ-phenylhexanoic acid which separated was extracted with ether. The ethereal solution was dried (Na_2SO_4) and evaporated. Benzene (3 × 100 c.c.) was caused to distil from the residue and finally traces of benzene were removed by heating under diminished pressure at 100°. The yellow oily residue (10·26 g.) partly solidified when kept. Titration with alkali showed that it contained unchanged acid. Toluene was added and distilled off slowly. The residue was kept at 100°/5 mm. for 8 hours and was found to contain 90% of lactone and to have α_{5780}^{25} −0·08° (*l* = 2; *c*, 15·418 in ethyl alcohol). For analytical purposes, the crude lactone was purified by extracting its ethereal solution with aqueous sodium carbonate and drying (Na_2SO_4). Removal of the ether, followed by vacuum-drying over calcium chloride and paraffin wax, gave *δ-phenyl-δ-hexanolactone*, m. p. 62°, $[\alpha]_{5780}^{25}$ −0·22°, $[\alpha]_{5461}^{25}$ −0·24° (*l* = 2; *c*, 12·033 in ethyl alcohol) (Found: C, 75·2; H, 7·5. $C_{12}H_{14}O_2$ requires C, 75·8; H, 7·4%).

In two other experiments on ¼ of the above scale, the Grignard reagent was added to the ester solution at 0°. In the first, addition was effected (shaking) during 1 minute and in the second during ½ hour. When worked up as just described, the first gave a lactone, m. p. 70—72°, $[\alpha]_{5780}^{25}$ −2·21°, $[\alpha]_{5461}^{25}$ −2·52° (*c*, 5·626), and the second a lactone, m. p. 68—71°, $[\alpha]_{5780}^{25}$ −1·32°, $[\alpha]_{5461}^{25}$ −1·47°.

Partial Asymmetric Synthesis of δ-Hydroxy-δ-phenylheptanoic Acid.—An ethereal solution of phenylmagnesium bromide (0·10 g.-mol.) was added to a solution of (−)-menthyl δ-acetylvalerate (22·6 g., 0·08 g.-mol.) in ether (80 c.c.) during 30 minutes, with ice-cooling and stirring. Cooling and stirring were continued for a further hour and the mixture was then kept at 0° for 12 hours. It was worked up by methods similar to those already described, *δ-hydroxy-δ-phenylheptanoic acid* being obtained (84% yield) as a pale yellow viscous oil (Found: C, 70·3; H, 8·2. $C_{13}H_{18}O_3$ requires C, 70·2; H, 8·2%). The acid had α_{5780} +0·09° (*l* = 2; *c*, 50 in ethyl alcohol).

Interaction of (−)-Menthyl ω-Acetylpelargonate and Phenylmagnesium Bromide.—An ethereal solution of phenylmagnesium bromide (0·1 g.-mol.) was added during ½ hour to an ice-cooled solution of (−)-menthyl ω-acetylpelargonate (27·04 g., 0·08 g.-mol.) with stirring. After 12 hours (0°) the product was worked up as usual and gave 22 g. of impure 10-hydroxy-10-phenylundecanoic acid. Since the acid was optically inactive, the experiment was not further pursued.

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710. *Partial Asymmetric Synthesis with Keto-esters. Part II.**

By DOREEN M. BOVEY and E. E. TURNER.

Interaction of methylmagnesium bromide with (−)-menthyl β-benzoylpropionate and γ-benzoyl-*n*-butyrate is accompanied by partial asymmetric synthesis.

IT was shown by McKenzie (*J.*, 1904, **85**, 1249) that interaction of methylmagnesium iodide and (−)-menthyl benzoylformate was accompanied by partial asymmetric synthesis, the atrolactic acid obtained after removal of the fixed centre of asymmetry, *i.e.*, the(−)-menthyl group, being lævorotatory:

$$Ph\cdot CO\cdot CO_2\cdot \overset{(-)}{C_{10}H_{19}} \xrightarrow[\text{etc.}]{MeMgI} Ph\cdot CMe(OH)\cdot CO_2\cdot \overset{(-)}{C_{10}H_{19}} \longrightarrow Ph\cdot CMe(OH)\cdot CO_2H$$

The present communication describes the analogous sets of reactions starting with methylmagnesium bromide and a series of (−)-menthyl esters, $Ph\cdot CO\cdot [CH_2]_n\cdot CO_2\cdot \overset{(-)}{C_{10}H_{19}}$ (*n* = 0, 2, 7, 4, and 8). The hydroxy-acids ultimately isolated were examined optically, either as such or as the lactones, if the latter were obtainable. All operations were carried out on a quantitative basis and were designed to ensure minimal loss of hydroxy-acid at any manipulative stage. The Grignard reactions were all performed in nitrogen, in the same all-glass apparatus, so as to secure reproducibility of results.

In order to link the present work with that of McKenzie (*loc. cit.*), we first treated (−)-menthyl benzoylformate with 1·25 molecular proportions of methylmagnesium bromide. Under our conditions, the atrolactic acid obtained (in 97% yield) had a specific rotation of $[\alpha]_{5780}^{25}$ −8·5° in absolute ethyl alcohol, whereas McKenzie, using one molecular proportion of methylmagnesium iodide, obtained an acid having $[\alpha]_D^{12}$ −8·3°. Evidently the change from

* Part I, preceding paper.

methylmagnesium iodide to the bromide and the slightly different experimental conditions had very little effect on the extent of asymmetric synthesis.

In the reactions starting with (−)-menthyl β-benzoylpropionate and methylmagnesium bromide, a preponderance of (−)-γ-hydroxy-γ-phenyl-*n*-valeric acid has been found to be produced; the corresponding lactone was dextrorotatory. When 1·25 molecular proportions of Grignard reagent to one of menthyl benzoylpropionate were used, the final acid contained considerable quantities of β-benzoylpropionic acid, either owing to incomplete reaction or to reaction of the enolic form of the ester :

$$Ph\cdot CO\cdot[CH_2]_2\cdot CO_2\cdot C_{10}H_{19} \rightleftharpoons Ph\cdot C(OH){:}CH\cdot CH_2\cdot CO_2\cdot C_{10}H_{19} \xrightarrow{MeMgBr} \xleftarrow[H_2O]{} Ph\cdot C(O\cdot MgBr){:}CH\cdot CH_2\cdot CO_2\cdot C_{10}H_{19}$$

By using two molecular proportions of Grignard reagent this was almost entirely suppressed, but a small amount of the glycol, $Ph\cdot CMe(OH)\cdot[CH_2]_2\cdot CMe_2\cdot OH$, was produced as a result of reaction at the carbomenthyloxy-group. For optical examination the final hydroxy-acid was converted into its lactone. The degree of asymmetric synthesis was found to be dependent only to a slight extent on the conditions under which the initial Grignard reactions were carried out. A short boiling of the reaction mixture after addition was complete gave a lactone with a slightly higher rotation ($[\alpha]^{25}_{5461}$ +10·2°) than that (+9·3°) of the product of a reaction mixture which had never been heated above 0°.

Fractional acidification of an aqueous alkaline solution of partially active γ-hydroxy-γ-phenylvaleric acid effected some resolution. Thus on acidification to pH 5, acid was precipitated with $[\alpha]^{25}_{5461}$ −4·42°, giving a lactone with $[\alpha]^{25}_{5461}$ +46·8°. Further acidification caused precipitation of acid with $[\alpha]^{25}_{5461}$ +2·56° (compare Part I, preceding paper).

Interaction of (−)-menthyl β-benzoylpropionate and 2 molecular proportions of ethylmagnesium bromide, followed by the usual treatment of the reaction mixture, led to slightly lævorotatory 4-hydroxy-4-phenylhexanoic acid,* the lactone of which was dextrorotatory. The (±)-acid melted at 89° (Trivedi and Nargund, *J. Univ. Bombay*, 1941, **10**, Part 3, p. 99, give 102—103°).

(−)-Menthyl γ-benzoyl-*n*-butyrate reacted almost quantitatively with methylmagnesium bromide (1·25 molecular proportions). The δ-hydroxy-δ-phenylhexanoic acid finally isolated was feebly lævorotatory but gave a lactone with $[\alpha]^{25}_{5461}$ +2·9° ± 0·1°. Partial resolution of the acid could be effected by using the brucine salt, the highest rotation recorded of the derived lactone being $[\alpha]^{25}_{5461}$ +15·7° in chloroform.

No evidence of partial asymmetric synthesis was observed in the interaction of methyl- or ethyl-magnesium bromide and (−)-menthyl δ-benzoyl-*n*-valerate. In view, however, of the low rotatory power of 4-hydroxy-4-phenylhexanoic acid, that of 6-hydroxy-6-phenylheptanoic acid may be assumed also to be slight and in the case of the second acid lactonisation could not be used to magnify the observable rotation.

(−)-Menthyl ω-benzoylpelargonate and methylmagnesium bromide led to 10-hydroxy-10-phenylundecanoic acid, which had no detectable optical activity.

Experimental.

General Method of Preparation of (−)-Menthyl Esters.—This was carried out essentially by McKenzie's method (*loc. cit.*). A mixture of the keto-acid (1 mol.) and 3—4 mols. of (−)-menthol was heated at 100° for about 9 hours, with occasional passage of hydrogen chloride. The reaction mixture was dissolved in ether, and the solution washed first with 10% aqueous sodium carbonate solution and then with water. The ethereal layer was evaporated and the residue freed from menthol by distillation in steam. The residual ester was crystallised or distilled until its specific rotation and rotatory dispersion ($\lambda_{5780} : \lambda_{5461}$) were constant. Unless otherwise stated, specific rotations were determined in absolute ethyl alcohol at 25° ($l = 2$).

General Procedure in Grignard Reactions.—The Grignard reagent was prepared in an all-glass apparatus previously dried at 130° and set up while still hot, with drying tubes (calcium chloride–soda-lime) in position. The magnesium used was dried at 130° and the methyl bromide over calcium chloride at 0°. The ether was dried over sodium wire. Air in the apparatus was replaced by nitrogen. After the Grignard reagent had been prepared, it was filtered through glass wool inside the apparatus and added drop by drop to a solution of 5 g. of keto-ester in 20 c.c. of ether with continous shaking and (usually) ice-cooling. Conditions were varied from one series of experiments to another as regards the time allowed to elapse before the reaction product was treated with ice and hydrochloric acid. The ethereal layer was separated and the aqueous layer extracted thrice with 10 c.c. of ether. The total combined ethereal solution was washed with 10 c.c. of water and dried (Na_2SO_4). The ether was distilled off and the residue dried in a vacuum for 30 minutes. It was weighed and then hydrolysed

* Geneva nomenclature ($CO_2H = 1$).

with boiling aqueous alcoholic potassium hydroxide. The alcohol was distilled off and the remaining mixture of menthol, neutral products, and alkaline solution was extracted four times with 10 c.c. of ether and then once with 20 c.c. of ether. In all experiments the last extract was optically inactive, proving the absence of menthol. The alkaline solution was freed from ether by warming and then cooled and acidified with 25% sulphuric acid. If a solid acid was precipitated it was filtered off, washed, and dried in a vacuum over calcium chloride. If an oily acid was obtained, it was extracted with ether (5 × 10 c.c.), the (dried) ethereal solution being evaporated and the residue kept in a vacuum over calcium chloride and paraffin wax. It was usually necessary to warm the products several times and repeat the vacuum-drying in order to remove the last traces of water and ether.

Interaction of (−)-Menthyl Benzoylformate and 1·25 Molecular Proportions of Methylmagnesium Bromide.—The Grignard reagent prepared from 0·525 g. of magnesium (ether, 20 c.c.) was added during 7 minutes, with shaking, to an ice-cooled solution of 5 g. of (−)-menthyl benzoylformate in 20 c.c. of ether. The mixture was then boiled under reflux for ½ hour. When cold, it was treated with ice (15 g.) and 25% hydrochloric acid (35 c.c.). The atrolactic acid finally obtained (2·48 g., 97%) had $[\alpha]^{25}_{5790}$ −8·5°, $[\alpha]^{25}_{5461}$ −9·3° (*c*, 12·40 in absolute ethyl alcohol). *(−)-Menthyl β-benzoylpropionate*, after being crystallised four times from light petroleum (b. p. 60—80°), had m. p. 92°, $[\alpha]^{25}_{5461}$ −62·1°, $[\alpha]^{25}_{5790}$ −54·8° (*c*, 1·715 in chloroform) (Found: C, 75·8; H, 8·9. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%).

Interaction of (−)-Menthyl β-Benzoylpropionate with Methylmagnesium Bromide (x Mols.).—(*a*) x = 1·25. The Grignard reagent prepared from 0·480 g. of magnesium, methyl bromide, and ether (20 c.c.) was added with shaking, during 10 minutes, to an ice-cooled solution of 5 g. of (−)-menthyl β-benzoylpropionate in 20 c.c. of ether. The mixture was boiled under reflux for 1½ hours, cooled, and treated with 20 g. of ice and 2 c.c. of concentrated hydrochloric acid. The γ-hydroxy-γ-phenylvaleric acid obtained had m. p. 96—98°, $[\alpha]^{25}_{5461}$ −0·07° (*c*, 4·115 in absolute alcohol). Evaporation of the rotation solution in presence of a drop of dilute hydrochloric acid gave the lactone with $[\alpha]^{25}_{5461}$ +6·0° (*c*, 3·75 in absolute alcohol). In a similar experiment the lactone had $[\alpha]^{25}_{5461}$ +6·7° (l = 2; *c*, 6·20 in absolute alcohol).

(*b*) x = 2. Sixteen different experiments were carried out in which the time of addition of Grignard reagent was varied from 0 to 15 minutes and subsequent treatment, before treatment with ice and acid, was varied between keeping at 0° for 3 hours and boiling under reflux for 1½ hours. The rotations of the lactones ultimately isolated varied from $[\alpha]^{25}_{5461}$ +9·0° to +10·5° (*c*, about 6·5 in absolute ethyl alcohol).

An experiment was performed on 25 g. of keto-ester, using 2 mols. of methylmagnesium bromide. The reaction mixture was worked up in the usual way and the product of alkaline hydrolysis, after removal of menthol, was made up to 100 c.c. This solution was divided into three portions which were treated as follows: (1) 25 c.c. were acidified with sulphuric acid and extracted with ether. The lactone was prepared and was found to have $[\alpha]^{25}_{5461}$ +9·0° (*c*, 8·30 in alcohol). (2) 25 C.c. were acidified and the acid (1·65 g.; m. p. 100—102°) was filtered off and dried. It had $[\alpha]^{25}_{5461}$ −1·30° (*c*, 8·1 in alcohol). The lactone prepared from this acid had $[\alpha]^{25}_{5461}$ +12·2° (*c*, 6·2) suggesting that precipitation of the acid from its alkaline solution resulted in preferential precipitation of the optically active isomeride present in excess in the mixture. (3) 50 C.c. were acidified and the acid (3·41 g.; m. p. 99—101°) was filtered off and dried. The products from (1), (2), and (3) were combined and dissolved in 10% aqueous potassium hydroxide. By acidification of this solution to pH 5—6, 1·3 g. of acid, m. p. 109°, were obtained, having $[\alpha]^{25}_{5461}$ −4·42°, giving a lactone with $[\alpha]^{25}_{5461}$ +46·7° (*c*, 3·475 in alcohol). The ratio $[\alpha]_{\text{lactone}} : [\alpha]_{\text{acid}} = -10·5$. Acidification of the mother-liquor to methyl-orange gave 1·25 g. of acid, m. p. 102—103°, having $[\alpha]^{25}_{5461}$ +2·56° (*c*, 5·86 in alcohol), giving a lactone with $[\alpha]^{25}_{5461}$ −22·2° (*c*, 5·3). This crop was slightly contaminated with β-benzoylpropionic acid, which accounts for the low ratio, $[\alpha]_{\text{lactone}} : [\alpha]_{\text{acid}}$ of −9·1.

A second experiment on the same scale was performed, in an attempt to extend the above technique to effect a separation of the acid into its two optical isomerides, but although a lævorotatory acid of 90% optical purity was obtained, the pure form was not isolated.

Reaction between (−)-Menthyl β-Benzoylpropionate and Ethylmagnesium Bromide.—Four experiments were performed, using 5 g. of the keto-ester and 2 mols. of Grignard reagent. A slightly lævorotatory 4-hydroxy-4-phenylhexanoic acid was obtained, giving a lactone with $[\alpha]^{25}_{5461}$ +8·47° (*c*, 5·9 in alcohol). The acid, recrystallised from carbon tetrachloride, had m. p. 89° (cf. Trivedi and Nargund, *J. Univ. Bombay*, **10**, Part 3, 99—107, who give m. p. 102—103°) (Found: C, 69·2; H, 7·8. Calc. for $C_{12}H_{16}O_3$: C, 69·2; H, 7·75%).

1-*Phenylcyclopentene*. A solution of *cyclo*pentanone (61 g., 0·5 g.-mol.) in ether (250 c.c.) was added during 1 hour with stirring and ice-cooling to a Grignard reagent made from bromobenzene (1 g.-mol.) (1 l. of ether). Stirring was continued for a further 1½ hours and the mixture kept overnight. It was decomposed in the standard way. The ethereal layer and subsequent ethereal extracts of the aqueous layer were washed with aqueous alkali and with water. The dried (Na_2SO_4) ethereal solution was distilled at atmospheric pressure and later at 30 mm. until no more water distilled. The pressure was then decreased to 4 mm., 1-phenyl*cyclo*pentene distilling 84° (m. p. 23°; yield 75%).

γ-*Benzoylbutyric Acid*.—A solution of 1-phenyl*cyclo*pentene (5 g.) in glacial acetic acid (200 c.c.) was stirred and powdered chromic anhydride (15 g.) added in small portions during 10 minutes. Thereafter stirring was continued for 50 minutes, and water and ether (200 c.c. each) were added. After vigorous shaking the mixture was kept until it separated into two layers, more water being added if necessary. The aqueous layer was extracted 4 times with 100 c.c. of ether, and the total ethereal solution extracted thrice with 100 c.c. of water and then with 200 c.c. of 5% aqueous sodium hydroxide. These extracts were discarded as containing mainly chromic and acetic acids. The ether was then extracted twice with 500 c.c. of 10% sodium hydroxide solution. This extract consisted

mainly of chromic and acetic acids, but was acidified with concentrated hydrochloric acid to recover the traces of γ-benzoylbutyric acid present. The bulk of the γ-benzoylbutyric acid was then extracted with 2 × 50 c.c. 10% aqueous sodium hydroxide and finally with 50 c.c. of water. These combined extracts were poured slowly into concentrated hydrochloric acid and the precipitated acid was filtered off and dried *in vacuo* (P_2O_5). Recrystallisation from water gave γ-benzoylbutyric acid, m. p. 126·5—127°. Fieser and Szmuszkovicz (*J. Amer. Chem. Soc.*, 1948, **70**, 3352), by chromic–acetic acid oxidation of 1-phenylcyclopentan-1-ol, obtained material of m. p. 126°.

(−)-*Menthyl γ-benzoylbutyrate* was caused to crystallise by cooling a solution in light petroleum (b. p. 40—60°) in solid carbon dioxide–alcohol. Four such processes gave a product, m. p. 18·5—19·0°, with $[\alpha]_{5461}^{25}$ −59·9°, $[\alpha]_{5780}^{25}$ −52·7° (*c*, 1·560 in alcohol) (Found: C, 76·4; H, 9·6. $C_{21}H_{30}O_3$ requires C, 76·4; H, 9·2%).

Interaction of (−)-*Menthyl γ-Benzoylbutyrate with Methylmagnesium Bromide.*—(a) *With* 1·25 *molecular proportions of Grignard reagent.* Five separate experiments were made, the extreme variation in conditions being (1) to add the Grignard reagent to the ethereal ester solution at 0° and keep the mixture at 0° for a further 3 hours and (2) to add the Grignard reagent to the boiling ethereal ester solution and continue to boil it for a further ½ hour. The reaction mixture was worked up as usual and the product hydrolysed with aqueous-alcoholic potassium hydroxide. Menthol was removed by ether-extraction and the alkaline solution then acidified and extracted with ether. The (dried) ethereal extract was evaporated. The acids obtained had a low rotation and were therefore converted into the lactone by evaporating a solution in alcohol–benzene or in benzene. The yield of δ-hydroxy-δ-phenylhexanoic acid, m. p. *ca.* 76°, only varied from 86 to 89%, but the specific rotation of the corresponding lactone (m. p. *ca.* 73°) was $[\alpha]_{5461}^{25}$ +2·1° (*c*, 11·25) when the reaction was carried out entirely at 0°, and $[\alpha]_{5461}^{25}$ +2·8° to +3·0° (*c*, 12) when the reaction mixture was boiled under reflux.

(b) *With* 2 *molecular proportions of Grignard reagent.* The lactone isolated had, in one experiment, $[\alpha]_{5461}^{25}$ +2·40° (*c*, 8·85) and in a second $[\alpha]_{5461}^{25}$ +2·20° (*c*, 7·80) (yields, 69 and 67% respectively). A sample of the *lactone* obtained in these experiments crystallised in plates from alcohol, m. p. 70—71° (Found: C, 75·5; H, 7·3. $C_{12}H_{14}O_2$ requires C, 75·8; H, 7·4%).

Interaction of (−)-menthyl γ-benzoylbutyrate and ethylmagnesium bromide led to an oily lactone which was optically inactive.

(±)-*δ-Hydroxy-δ-phenylhexanoic Acid.*—(*a*) A Grignard reagent (1·5 mols.) prepared from methyl bromide (17 g.) was added with stirring to ethyl γ-benzoylbutyrate (22 g., 1 mol.) in ether. The reaction was completed by boiling and the mixture worked up normally. The crude hydroxy-ester obtained was hydrolysed with aqueous alcoholic alkali. The alkaline solution was freed from by-products by ether-extraction and acidified. The oil precipitated soon solidified and was crystallised from benzene below 40° to prevent lactonisation. The *acid* (11 g., 53%) had m. p. 73—74° (Found: C, 68·8; H, 7·4. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

(*b*) A Grignard reagent prepared from bromobenzene (56 g.) was added at 0° to an ethereal solution of ethyl γ-acetylbutyrate (45 g.). The pure acid finally obtained (20 g., 30%) had m. p. 73—74°.

Partial Optical Resolution of δ-Hydroxy-δ-phenylhexanoic Acid.—Brucine formed a crystalline salt which was crystallised from water four times, the rotation falling from $[\alpha]_{5461}^{25}$ −48·2° to −43·1° in chloroform (*c*, 0·60), the m. p. rising from 106—108° to 108—110°. The salt was stirred at 0° with hydrochloric acid, and 10% aqueous sodium hydroxide added later. The brucine was extracted with chloroform, and the alkaline layer acidified; the acid was extracted with ether, which was then removed in a vacuum. Conversion into lactone was effected by boiling a benzene solution of the residue and subsequently removing the benzene in a vacuum. The lactone had $[\alpha]_{5461}^{25}$ +15·67° in chloroform (*c*, 3·695).

(−)-*Menthyl δ-Benzoyl-n-valerate.*—Prepared from the acid, obtained by Hill's method (*J. Amer. Chem. Soc.*, 1932, **54**, 4106), the *ester* crystallised from ether at the temperature of solid carbon dioxide–alcohol and had m. p. 50°, $[\alpha]_{5461}^{25}$ −59·5°, $[\alpha]_{5780}^{25}$ −52·6° (*c*, 1·650 in absolute ethyl alcohol) (Found: C, 76·6; H, 9·3. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·4%).

Interaction of (−)-*Menthyl δ-Benzoylvalerate with Methylmagnesium Bromide.*—(a) *With* 1·25 *mols. of Grignard reagent.* The reaction was performed at 0°, followed by boiling for ½ an hour. The δ-hydroxy-δ-phenylheptanoic acid (yield, 97—98% in different experiments) formed by hydrolysis of the menthyl ester was optically inactive.

(b) *With* 2 *mols. of Grignard reagent* [otherwise, reaction conditions as in (a)]. The hydroxy-acid obtained (yield, 69—72% in different experiments) had α_{5461}^{26} +0·08° (*c*, 11·0 in ethyl alcohol).

(c) *With* 4 *mols. of Grignard reagent* [otherwise, reaction conditions as in (a)]. The hydroxy-acid obtained (yield, 43%) was optically inactive.

Interaction of (−)-*Menthyl δ-Benzoylvalerate with Ethylmagnesium Bromide.*—By use of 1·25 mols. of Grignard reagent an inactive hydroxy-acid was obtained. With 2 mols. of Grignard reagent an acid was obtained with α_{5461}^{26} −0·03° in alcohol (*c*, 12·85).

ω-Benzoylpelargonic Acid.—This was prepared by the Friedel–Crafts reaction between ω-carbethoxynonoyl chloride and benzene, in presence of aluminium chloride, followed by hydrolysis of the ethyl ω-benzoylpelargonate so obtained (see Papa, Schwenk, and Hankin, *J. Amer. Chem. Soc.*, 1947, **69**, 3018).

(−)-*Menthyl ω-benzoylpelargonate* (10-*keto*-10-*phenyldecanoate*) had b. p. 250°/1·5 mm. Crystallised from ethyl alcohol, it had m. p. 37—38°, $[\alpha]_{5461}^{24}$ −51·05° (*c*, 2·145 in absolute ethyl alcohol) (Found: C, 78·0; H, 10·4. $C_{29}H_{46}O_3$ requires C, 78·0; H, 10·1%).

Interaction of the Foregoing Menthyl Ester with Methylmagnesium Bromide.—This reaction gave a product from which only optically inactive 10-*hydroxy*-10-*phenylundecanoic acid* was obtained. Crystallised from light petroleum (b. p. 60—80°), it had m. p. 61—62° (Found: C, 73·5; H, 9·0. $C_{17}H_{26}O_3$ requires C, 73·4; H, 9·4%).

Interaction of Menthyl Benzoylpelargonate with Ethylmagnesium Bromide.—This gave rise to 11-hydroxy-11-phenyldodecanoic acid with a small but definite optical activity: $[\alpha]_{5461}^{28}$ −0·05° (*c*, 13—14 in alcohol).

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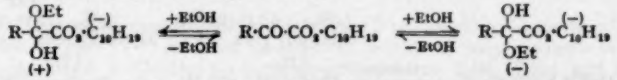
711. *Partial Asymmetric Synthesis with Keto-esters. Part III.**

By DOREEN M. BOVEY, JOAN A. REID, and E. E. TURNER.

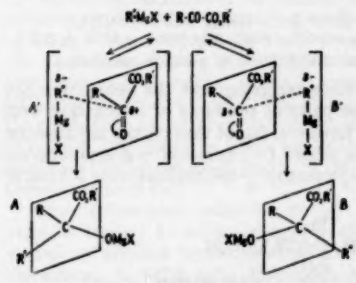
The experimental results described in Parts I and II are correlated. In partial asymmetric syntheses originating in interaction of Grignard reagents and the (−)-menthyl esters of α-, γ-, and δ-keto-acids the controlling factor is the extent of equilibration in the transition complex which is postulated as preceding the formation of the magnesium compound and is, in many cases, modified by precipitation of the product.

IN Parts I and II (preceding papers) are described investigations into the extent of partial asymmetric synthesis occurring during the action of certain Grignard reagents on (−)-menthyl esters of some keto-acids.

The idea that the carbonyl group in the (−)-menthyl ester of an α-keto-acid could be stereospecifically polarised (induced asymmetry) appears to be dismissed by the results of Jamison and Turner (*J.*, 1941, 538) and of Glazer and Turner (*J.*, 1949, S 169) in their study of the mutarotation of such esters in alcoholic solution, it being shown that hemi-acetal formation sufficiently accounts for the observed phenomena:



That there is a strong *chemical* influence by the ester group on the α-keto-group is shown by the fact of this hemi-acetal formation, which is peculiar to α-keto-esters; when methylene groups are interposed between the keto-group and the ester group any chemical inductive or electromeric effect between these groups is damped out.



In the case of the mutarotation of alcoholic solutions of (−)-menthyl esters of α-keto-acids, a real equilibrium can be attained between the hemi-acetals. An "asymmetric reaction" (Turner and Harris, *Quart. Reviews*, 1947, **1**, 299) occurs, but it cannot be made the precursor of an asymmetric *synthesis* since the hemi-acetals exist only in solution in presence of excess of alcohol, and removal of the (−)-menthyl group, such as would be necessary in order to provide a formal partial asymmetric synthesis, is meaningless.

In the well-established partial asymmetric syntheses (McKenzie and his co-workers, references in Parts I and II) which occur as a result of the interaction of Grignard reagents and the (−)-menthyl esters of α-keto-acids, equilibration must presumably take place to some extent at the transition complex stage (see inset), before precipitation of the magnesium complexes.

The discovery (Reid and Turner, *J.*, 1949, 3365) that the interaction of acetophenone, zinc, and (−)-menthyl bromoacetate is accompanied by partial asymmetric synthesis bears strongly on this point. In the present work the partial asymmetric synthesis observed with (−)-menthyl benzoylformate and methylmagnesium bromide leads to a product, atrolactic acid, which is largely antimeric with that produced in the partial asymmetric synthesis

* Part II, preceding paper.

involving (−)-menthyl pyruvate and phenylmagnesium bromide. On use of 1·25 molecular proportions of Grignard reagent to one of ester, the first route gave atrolactic acid with $[\alpha]_{5461}^{26}$ −9·3° and the second route an acid with $[\alpha]_{5461}^{20}$ +8·1° (rotations in absolute ethyl alcohol). By the second route, however, the yield of acid was only 50% owing to interaction of the Grignard reagent with the ester grouping (glycol formation), whereas by the first route a 97% yield of atrolactic acid was obtained. It is therefore impossible to assess the significance of the rotation figures.

In comparison with the present results it may be noted that McKenzie and Ritchie (*Biochem. Z.*, 1932, **250**, 376) investigated the partial asymmetric synthesis of 4-methoxyatrolactic acid by two routes. Interaction of (−)-menthyl *p*-methoxybenzoylformate and methylmagnesium iodide gave a final acid with $[\alpha]_{5461}^{25}$ −15·9°, whereas interaction of (−)-menthyl pyruvate and *p*-methoxyphenylmagnesium bromide led to an acid with $[\alpha]_{5461}^{25}$ +9·4° :

$$MeO\cdot C_6H_4\cdot CO\cdot CO_2\cdot C_{10}^{(-)}H_{19} \xrightarrow[\text{etc.}]{MeMgI} MeO\cdot C_6H_4\cdot CMe(OH)\cdot CO_2H\ [\alpha]_{5461}^{25} -15\cdot9^\circ$$

(Optically pure, $[\alpha]_{5461}^{25}$ −61·7°)

$$Me\cdot CO\cdot CO_2\cdot C_{10}^{(-)}H_{19} \xrightarrow[\text{etc.}]{MeO\cdot C_6H_4\cdot MgBr} MeO\cdot C_6H_4\cdot CMe(OH)\cdot CO_2H\ [\alpha]_{5461}^{25} +9\cdot4^\circ$$

(Optically pure, $[\alpha]_{5461}^{25}$ +61·0°)

Since in these cases the degree of possible partial asymmetric synthesis depends on the difference in thermodynamic stability of the two diastereoisomeric transition complexes, a similar state of affairs should obtain when Grignard reagents react with (−)-menthyl esters of keto-acids other than those of the α-type.

Partial asymmetric synthesis has not hitherto been observed in the interaction of γ-keto-esters of active alcohols with Grignard reagents. We find that the possibility is realisable, as the following results show :

$$CH_3\cdot CO\cdot[CH_2]_3\cdot CO_2\cdot C_{10}^{(-)}H_{19} \xrightarrow[\text{etc.}]{PhMgBr,} CH_3\text{–}\overset{\displaystyle Ph}{\underset{\displaystyle OH}{C}}\text{–}[CH_2]_3\cdot CO_2H \longrightarrow CH_3\text{–}\overset{\displaystyle Ph}{\underset{\displaystyle O}{C}}\!\!<\!\!\begin{matrix}CH_2\\ CH_2\\ CO\end{matrix}$$

$[\alpha]_{5461}^{25}$ +0·73° (EtOH) (Optically pure, +5·7°) $[\alpha]_{5461}^{25}$ −7·7° (EtOH) (Optically pure, −61·9° ± 0·4°)

$$Ph\cdot CO\cdot[CH_2]_3\cdot CO_2\cdot C_{10}^{(-)}H_{19} \xrightarrow[\text{etc.}]{MeMgBr} Ph\text{–}\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}\text{–}[CH_2]_3\cdot CO_2H \longrightarrow Ph\text{–}\overset{\displaystyle CH_3}{\underset{\displaystyle O}{C}}\!\!<\!\!\begin{matrix}CH_2\\ CH_2\\ CO\end{matrix}$$

$[\alpha]_{461}^{25}$ −0·97° (EtOH) (Optically pure, −5·7°) $[\alpha]_{5461}^{25}$ +10·2° (EtOH) (Optically pure, +61·8° ± 0·5°)

(Rotations for the acid relate to material obtained by total acidification of alkaline solutions.)

With increasing numbers of carbon atoms between the ester group and the keto-group the difference between the thermodynamic stabilities of the pairs of products of interaction with Grignard reagents must gradually decrease. We have, however, found that partial asymmetric synthesis of 5-hydroxy-5-phenylhexanoic acid occurs when (−)-menthyl γ-acetylbutyrate is treated with phenylmagnesium bromide and when (−)-menthyl γ-benzoylbutyrate is treated with methylmagnesium bromide :

$$CH_3\cdot CO\cdot[CH_2]_3\cdot CO_2\cdot C_{10}^{(-)}H_{19} \xrightarrow[\text{etc.}]{PhMgBr} CH_3\text{–}\overset{\displaystyle Ph}{\underset{\displaystyle OH}{C}}\text{–}[CH_2]_3\cdot CO_2H$$

Lactone : $[\alpha]_{5461}^{25}$ −2·52° (EtOH)

$$Ph\cdot CO\cdot[CH_2]_3\cdot CO_2\cdot C_{10}^{(-)}H_{19} \xrightarrow[\text{etc.}]{MeMgBr} Ph\text{–}\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}\text{–}[CH_2]_3\cdot CO_2H$$

Lactone : $[\alpha]_{5461}^{25}$ +2·9° (EtOH)

The extent of partial asymmetric synthesis cannot be estimated since the rotations of the optically pure lactones are unknown.

Neither the interaction of (−)-menthyl ω-acetylpelargonate and phenylmagnesium bromide nor that of (−)-menthyl ω-benzoylpelargonate and methylmagnesium bromide was accompanied by measurable partial asymmetric synthesis.

The background to the present investigation is admirably given by Ritchie (*Adv. Enzymology*, 1947, **7**, 65. See also Tiffeneau, Lévy, and Ditz, *Compt. rend.*, 1931, **192**, 955; *Bull. Soc. chim.*, 1935, **5**, 1848, 1855; Roger, *J.*, 1939, 108; Brokaw and Brode, *J. Org. Chem.*, 1948, **13**, 194).

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BEDFORD COLLEGE, UNIVERSITY OF LONDON. [*Received, June 28th*, 1951.]

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712. *Organic Fluoro-compounds. Part V.* ω-Trihalogenoacetophenones.*

By W. B. WHALLEY.

The first portion of this communication describes novel syntheses of 2 : 6-dihydroxy-4-methoxyacetophenone (III), 2-methylphloroglucinol 5-methyl ether (VI), 4-hydroxy-2 : 6-dimethoxyacetophenone (VIII; R = Ac), 4-hydroxy-2 : 6-dimethoxybenzoic acid (VIII; R = CO_2H), and of several derivatives, by the application and extension of the work reported in Part IV.* The Hoesch synthesis with trichloromethyl cyanide and 4-hydroxy-3-methylcoumarone (XIII; R = H) furnished 4-hydroxy-3-methyl-2-trichloroacetylcoumarone (XIII; R = CO·CCl_3) whilst trifluoromethyl and trichloromethyl cyanides and 2-methylphloroglucinol 1-methyl ether gave rise to the ketones (XI; R = CF_3) and (XI; R = CCl_3), respectively. 2-Methylphloroglucinol 1 : 5-dimethyl ether (XII; R = H) similarly furnished the ketones (XII; R = CO·CF_3) and (XII; R = CO·CCl_3).

The theoretical implications of the bright colour and the reactions of the ω-trichloro- and ω-trifluoro-polyhydroxyacetophenones and their derivatives are discussed.

THE new and improved method for the preparation of 2 : 6-dihydroxy-4-methoxybenzaldehyde recently described (Part IV *) has been extended to provide an easy synthesis of the hitherto difficultly accessible 2 : 6-dihydroxy-4-methoxyacetophenone (III) (Sonn and Bulow, *Ber.*, 1925, **58**, 1691). The application of the Hoesch reaction with methyl cyanide to ω-trichloro-2 : 4-dihydroxy-6-methoxyacetophenone (I; R = CCl_3) (Part IV, *loc. cit.*) was not successful, but by the substitution of the methyl ester (I; R = OMe) the keto-ester (II) was obtained in moderate yield. The production of the keto-ester (II) from (I; R = OMe) by *C*-acetylation by using acetic anhydride in the presence of boron trifluoride proceeded quantitatively, as did the formation of (IV; R = CCl_3) from (I; R = CCl_3) by the same method. The alkaline hydrolysis of (II) or (IV; R = CCl_3) readily furnished 2 : 6-dihydroxy-4-methoxyacetophenone (III) in quantitative yield. The structures allocated to (II) and (IV; R = CCl_3) follow from the production of (III) by hydrolysis, and are further confirmed by the reduction of (IV; R = CCl_3) with zinc dust and acetic acid to the diketone (IV; R = Me), identical with an authentic specimen kindly provided by Dr. F. M. Dean of this Department (Dean and Robertson, forthcoming publication).

The Clemmensen reduction of (V; R = CHO) (Part IV, *loc. cit.*) readily gave rise in high yield to methyl 2 : 4-dihydroxy-6-methoxy-3-methylbenzoate (V; R = Me), which was converted by alkaline hydrolysis into 2-methylphloroglucinol 5-methyl ether (VI) (cf. Curd and Robertson, *J.*, 1933, 437; Robertson and Whalley, *J.*, in the press). The application of the Gattermann aldehyde synthesis to (V; R = Me) furnished methyl 5-formyl-2 : 4-dihydroxy-6-methoxy-3-methylbenzoate (VII).

The interaction of phloroglucinol dimethyl ether and trichloromethyl cyanide gave rise exclusively to the ketone (VIII; R = CO·CCl_3), unaccompanied by detectable quantities of the second possible isomeride (IX; R = CCl_3). The absence of the second ketone is remarkable in view of the well-established production of the two possible isomerides with a variety of other cyanides (Canter, Curd, and Robertson, *J.*, 1931, 1245). Phloroglucinol dimethyl ether and trifluoromethyl cyanide behaved normally and furnished a mixture of the isomeric ketones (VIII; R = CO·CF_3), and (IX; R = CF_3) which were readily separable by steam-distillation.

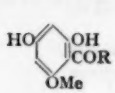
* Part IV, *J.*, 1951, 665.

Alkaline hydrolysis of (VIII; R = CO·CCl_3) furnished the acid (VIII; R = CO_2H), whilst Clemmensen reduction (Part IV, *loc. cit.*) readily gave rise to 2-ethylphloroglucinol 1 : 3-dimethyl ether (VIII; R = Et), thus providing a rapid and convenient means of access to these two compounds.

Reduction of ω-trichloro-4-hydroxy-2 : 6-dimethoxyacetophenone (VIII; R = CO·CCl_3) with zinc dust in acetic acid furnished 4-hydroxy-2 : 6-dimethoxyacetophenone (VIII; R = Ac) in high yield, thus providing an alternative route to this compound and obviating its separation from the isomeric ketone which is a necessary concomitant of the usual synthesis (Canter, Curd, and Robertson, *loc. cit.*).

In view of the propensity of the trichloroacetyl group for substitution in the *para*-position to a phenolic hydroxyl group, as indicated by the production of (VIII; R = CO·CCl_3) and of ω-trichloro-4-hydroxy-2-methoxyacetophenone (Part IV, *loc. cit.*), the application of the Hoesch synthesis with trichloromethyl and trifluoromethyl cyanides to 2-methylphloroglucinol 1-methyl ether and 2-methylphloroglucinol 1 : 5-dimethyl ether seemed of interest. With trichloromethyl cyanide and methylphloroglucinol 5-methyl ether substitution occurred in the normal position only with the production in low yield of ω-trichloro-2 : 6-dihydroxy-4-methoxy-3-methylacetophenone (XI; R = CCl_3). No trace of the second, expected isomeride could be detected. This is in accordance with the well-established behaviour of 2-methylphloroglucinol 1-methyl ether under the normal conditions of the Hoesch synthesis (compare Curd and Robertson, *J.*, 1933, 1173). The orientation of (XI; R = CCl_3) is established by the ready conversion into methyl 2 : 6-dihydroxy-4-methoxy-3-methylbenzoate (XI; R = OMe) under the conditions described in Part IV (*loc. cit.*).

Trifluoromethyl cyanide and 2-methylphloroglucinol 1-methyl ether gave rise to a good yield of only one isomeride, which by analogy with the corresponding derivative from trichloromethyl cyanide is represented by (XI; R = CF_3).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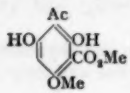
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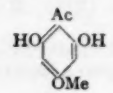
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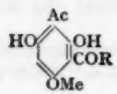
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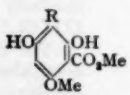
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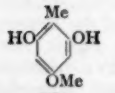
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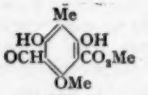
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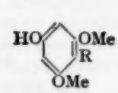
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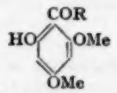
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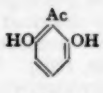
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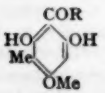
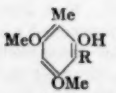

(XI)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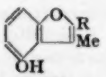
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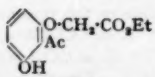
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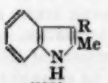

(XV)

In accordance with the previously observed behaviour of 2-methylphloroglucinol 1 : 5-dimethyl ether (Curd and Robertson, *loc. cit.*), trifluoromethyl and trichloromethyl cyanides with this phenol gave only the ketones (XII; R = CO·CF_3) and (XII; R = CO·CCl_3), respectively, the orientations of which were established by the ferric reactions in alcohol and by hydrolysis to the acid (XII; R = CO_2H). The trichloromethyl ketone (XII; R = CO·CCl_3) was obtained in small yield.

In view of the interesting implications, which are discussed more fully later, of the colours exhibited by the ω-trichloro- and ω-trifluoro-acetophenones, the preparation of 4-hydroxy-3-methyl-2-trichloroacetylcoumarone (XIII; R = CO·CCl_3) was carried out. The condensation of 2-acetylresorcinol (X) with ethyl bromoacetate readily furnished the phenoxy-ester (XIV) which was converted by the standard procedure into the coumarones (XIII; R = H) and (XIII; R = CO_2Et). The application of the Hoesch synthesis with trichloromethyl cyanide to (XIII; R = H) gave rise to (XIII; R = CO·CCl_3), but the reaction did not proceed as readily as in the case of the isomeric 6-hydroxy-4-methylcoumarone (Part IV, *loc. cit.*). This is not surprising in view of the well-recognised inactivity to this type of substitution of the 2-position of the resorcinol system, and the α-position of (XIII; R = H) is equivalent to the 2-position. Direct conversion of (XIII; R = CO·CCl_3) into (XIII; R = CO_2Et) (Part IV,

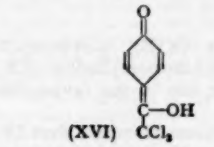
loc. cit.) gave rise to a product identical with that obtained by the direct cyclisation of (XIV) with sodium ethoxide, thus establishing the orientation of (XIII; R = CO·CCl_3).

The ready conversion of 2-methyl-3-trichloroacetylindole (XV; R = CO·CCl_3) into the corresponding methyl ester (XV; R = CO_2Me) is also reported and discussed later.

Discussion.

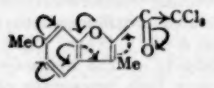
Several points concerning the chemistry of the ω-trichloro- and ω-trifluoropolyhydroxymethyl ketones described in this and the previous part (Part IV, *loc. cit.*) merit further discussion.

These compounds are often yellow and even brilliant yellow in colour and, in view of the non-chromophoric properties of the appropriate aromatic moieties and of the trichloroacetyl and trifluoroacetyl groups, the colour would seem to be ascribable to the presence of a quinonoid structure (*ortho* or *para*) of type (XVI), similar to that suggested by Hunsberger and Amstutz (*J. Amer. Chem. Soc.*, 1948, **70**, 671) to account for the properties of the electronically similar hydroxyphenylglyoxylic acids (compare Ralph and Robertson, *J.*, 1950, 3380). The driving force behind this change is presumably the very strong electrophilic nature of the trihalogenomethyl group which is more readily exerted in the quinonoid form. Further, the presence of the *ortho-para* directing hydroxyl and methoxyl groupings would be expected to enhance the stability of these quinonoid structures (compare Gomberg and West, *J. Amer. Chem. Soc.*, 1912, **34**, 1529). The solutions of these trihalogeno-ketones in alkali always have an intense



(XVI)

(XVII) (XVIII)



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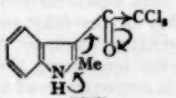

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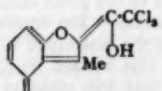
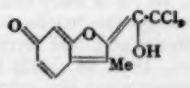


(XXI)



(XXII)

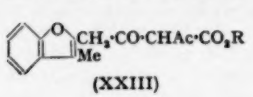
yellow colour presumably because the salts formed are those of the appropriate enol. The lack of normal carbonyl reactivity in the trihalogenoacetyl systems is due partially at least to this quinonoid system (compare the behaviour of the phenylglyoxylic acids), a view which is supported by the fact that there have now been prepared, albeit with difficulty, the 2 : 4-dinitrophenylhydrazones of ω-trifluoro-2 : 4-dimethoxyacetophenone and of 6-methoxy-2-trifluoroacetylcoumarone (Part IV, *loc. cit.*). The enolic hydroxyl group together with the quinonoid carbonyl in compounds of types (XVI), (XVII), and (XXII) constitute aromatic vinylogues of the carboxylic acid system, thus satisfactorily explaining the lack of normal activity of the quinonoid carbonyl group and the acidity of the enolic hydroxyl, a property which is enhanced by the electrophilic trihalogenomethyl residue. The very intense yellow colour of the ω-trihalogeno-*o*-hydroxyacetophenones is undoubtedly due to resonance between the two canonical structures of types (XVII) and (XVIII) producing resonance stabilisation of the *ortho*-quinonoid form with a consequent deepening of colour (compare Johnson, "Modern Electronic Concepts of Valence," Vol. II, p. 1870, of "Organic Chemistry" 2nd edn., Wiley, New York, 1943, edited by Gilman).

The bright yellow colours of 4- and 6-hydroxy-2-trihalogenoacetylcoumarones together with the deep orange colour produced in alcoholic sodium acetate solution, and the lack of colour exhibited by the 7-methoxy-2-trihalogenoacetylcoumarones (Part IV, *loc. cit.*) are indicative of the structures (XXI) and (XXII) for the hydroxy-compounds. By analogy with the resonance structures types (XVII) and (XVIII) allocated to the *o*-hydroxy-ω-trihalogenoacetophenones, the *p*-hydroxy-ketones and the benzofuranones (XXI) and (XXII) may be more accurately represented by the resonance structures types (XXIV) and (XXV) respectively, rather than as tautomers.* However, we prefer not to make a definite decision on this point at the moment. The case of transformation of the benzofuran system into this quinonoid type provides an interesting comparison with the cyclisation of 2-substituted

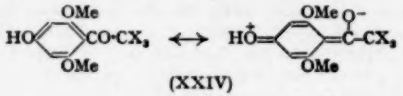
* We are indebted to one of the referees for emphasing this point.

coumarones of type (XXIII) to usnolic acids (Foster, Robertson, and Healey, *J.*, 1939, 1594) where related quinonoid intermediates may constitute the transition stage.

The work of Fischer and his co-workers (*inter alia*, *Ber.*, 1931, **64**, 240, 2636) has clearly shown that the hydrolytic fission of ω-trichloro-ketones (the haloform reaction) is catalysed by hydroxyl ions. The conversion of polyhydroxy-ω-trichloroacetophenones, 2-trichloroacetylcoumarones, and of 2-methyl-3-trichloroacetylindole into the corresponding methyl (and sometimes ethyl) esters in high yield (Part IV, *loc. cit.*, and the present paper) in the presence of methanol (or ethanol) containing a trace of aqueous potassium hydroxide is likewise catalytic. This simple reaction, which has not been previously described, although the conversion of ω-trichloroacetophenone into methyl benzoate in the presence of aqueous methanolic potassium hydroxide has been reported (Houben, *Ber.*, 1931, **64**, 2645), failed with 4-hydroxy-2-methoxy- and 4-hydroxy-ω-trichloro-2 : 6-dimethoxyacetophenone but proceeded with every ω-trichloro-*o*-hydroxyacetophenone examined.



(XXIII)



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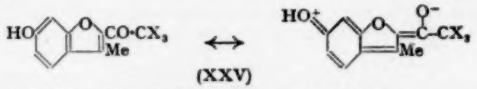
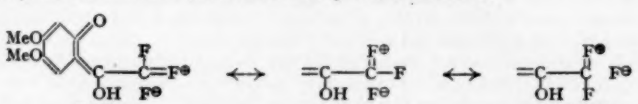


(XXV)

The ready conversion of 6-methoxy-2-trichloroacetylcoumarone (XIX), 4-hydroxy-2-trichloroacetylcoumarone (XIII; R = CO·CCl$_3$), and of 2-methyl-3-trichloroacetylindole (XX) into the corresponding methyl (and ethyl) carboxylic ester may be due to the favourable electromeric displacements initiated by the hetero-atoms.

The stability towards alkali of the ω-trifluoropolyhydroxyacetophenones (compare Part IV, *loc. cit.*) is in sharp contrast to the great facility with which the corresponding trichloro-ketones undergo the haloform reaction. The insolubility of the fully methylated ω-trifluoromethyl ketones no doubt increases the resistance to hydrolysis (compare Aston *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 1413) but this cannot be a factor influencing the stability of the hydroxy-compounds. We suggest that this stability is a consequence of the very high percentage of double bond character exhibited by the carbon–fluorine bond in the >CF$_2$ and −CF$_3$ residues (compare Pauling, "The Nature of the Chemical Bond," p. 235, Cornell University Press, 1948), and that this phenomenon influences the polar nature, and also the normal length of the carbon–carbon bond joining the trifluoromethyl carbon to the adjacent carbon atom (compare, *e.g.*, the abnormal Cl–C distance in trifluoromethyl chloride) with a reduction of the susceptibility of this carbon–carbon bond to heterolytic fission, *i.e.* to nucleophilic attack by the hydroxyl ion.

Further, resonance between the various possible structures, such as types (XXVI), (XXVII), and (XXVIII), will contribute additional stability to the molecule.*



(XXVI) (XXVII) (XXVIII)

This decreased reactivity towards nucleophilic displacement reactions also provides an explanation for the failure of the ω-trifluoroacetophenones to undergo conversion into carboxylic esters in a manner similar to the ω-trichloroacetophenones (Part IV, *loc. cit.*).

* The much greater stability towards decarboxylation of trifluoroacetic acid compared with trichloroacetic acid (Auerbach, Verhoek, and Henne, *J. Amer. Chem. Soc.*, 1950, **72**, 299) is also rationalised by the application of this theory. The three additional resonance forms for the trifluoroacetate ion enhance the resistance of the carbon–carbon bond to the heterolytic fission which occurs during decarboxylation:

$$CF_3 \cdot CO_2^{\ominus} \longrightarrow CF_3^{\ominus} + CO_2$$

(Auerbach, Verhoek, and Henne, *loc. cit.*; Johnson and Moelwyn-Hughes, *Proc. Roy. Soc.*, 1940, *A*, **175**, 118).

Similarly, as might be predicted, trifluoroacetaldehyde apparently undergoes the haloform reaction only "with strong aqueous bases" (Shechter and Conrad, *J. Amer. Chem. Soc.*, 1950, **72**, 3372).

Experimental.

2 : 6-*Dihydroxy-4-methoxyacetophenone* (III).—(*a*) A solution of methyl 2 : 4-dihydroxy-6-methoxybenzoate (Part IV, *loc. cit.*) (1·7 g.) in ether (100 ml.) containing zinc chloride (4 g.), methyl cyanide (10 ml.), and aluminium chloride (2 g.) was saturated at 5° with hydrogen chloride. 24 Hours later the semicrystalline ketimine salt was separated and dissolved in water (50 ml.), and the solution heated on the steam-bath for 20 minutes. The crystalline mass which separated from the cooled hydrolysate was collected and repeatedly recrystallised from methanol giving methyl 3-acetyl-2 : 4-dihydroxy-6-methoxybenzoate in long, slender needles, m. p. 170°, identical with the product from method (*b*).

When a solution of the previous partially purified keto-ester (1 g.) in water (15 ml.) containing potassium hydroxide (2 g.) was refluxed for 30 minutes, cooled, and acidified, 2 : 6-dihydroxy-4-methoxyacetophenone (0·6 g.) separated, m. p. 136°. Crystallisation from aqueous methanol gave the product in almost colourless needles, m. p. 137° (Found : C, 59·4; H, 5·3. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5%). Sonn and Bulow (*loc. cit.*) give m. p. 136°.

(*b*) A mixture of methyl 2 : 4-dihydroxy-6-methoxybenzoate (2·2 g.), acetic anhydride (0·7 g., 1·1 mol.), and acetic acid (15 ml.) was saturated with boron trifluoride (without cooling), whereupon the initially clear solution solidified to a yellow crystalline mass. Water (50 ml.) was then added and the suspended solid collected, washed with water, and dissolved in methanol (15 ml.), and the solution heated to boiling. The crystalline mass which separated on the addition of water was purified from a large volume of methanol to give *methyl 3-acetyl-2 : 4-dihydroxy-6-methoxybenzoate* (2·2 g.) in long, slender needles, m. p. 170° (Found : C, 55·1; H, 5·0. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%). Hydrolysis of this keto-ester as in (*a*) furnished a quantitative yield of 2 : 6-dihydroxy-4-methoxyacetophenone in needles.

(*c*) A mixture of ω-trichloro-2 : 6-dihydroxy-4-methoxyacetophenone (2 g.), acetic anhydride (0·7 g., 1 mol.), and acetic acid (5 ml.) was saturated with boron trifluoride (without cooling). The product was isolated as described in (*b*) and purified from aqueous methanol to give 2 : 6-*dihydroxy-4-methoxy-3-trichloroacetylacetophenone* (2·2 g.) in fawn-coloured needles, m. p. 115° (Found : C, 39·4; H, 3·5. $C_{11}H_9O_6Cl_3$ requires C, 40·3; H, 2·8%). Hydrolysis of this compound as described in (*a*) gave a quantitative yield of 2 : 6-dihydroxy-4-methoxyacetophenone in pink needles.

When a solution of the diketone (0·5 g.) in methanol (7 ml.) containing 1 drop of 60% potassium hydroxide solution was refluxed for 5 minutes and the product isolated in the normal way a quantitative yield of methyl 3-acetyl-2 : 4-dihydroxy-6-methoxybenzoate was obtained, identical with the compounds prepared by methods (*a*) and (*b*).

A suspension of the foregoing diketone in 2N-sodium hydrogen carbonate, containing a few drops of methanol, was warmed gently on the steam-bath whereupon a vigorous reaction occurred with the production of a clear solution and the evolution of chloroform. Isolation of the product and its purification from aqueous acetone furnished a quantitative yield of *3-acetyl-2 : 4-dihydroxy-6-methoxybenzoic acid*, m. p. 182° (decomp.) (Found : C, 53·1; H, 4·4. $C_{10}H_{10}O_6$ requires C, 53·1; H, 4·4%).

The reduction of 2 : 6-dihydroxy-4-methoxy-3-trichloroacetylacetophenone (0·5 g.) with zinc dust (1 g.) and acetic acid (5 ml.) on the steam-bath during 3 minutes furnished a quantitative yield of 3-acetyl-2 : 6-dihydroxy-4-methoxyacetophenone, m. p. 105°, identical with an authentic specimen.

Methyl 5-Formyl-2 : 4-dihydroxy-6-methoxy-3-methylbenzoate (VII).—Methyl 3-formyl-2 : 4-dihydroxy-6-methoxybenzoate was prepared by the following modification of the method previously described (Part IV, *loc. cit.*). A suspension of methyl 2 : 4-dihydroxy-6-methoxybenzoate (2·2 g.) in ether (120 ml.) containing zinc cyanide (1·5 g.) and hydrogen cyanide (10 ml.) was saturated with hydrogen chloride, and the product isolated as previously described to give the aldehyde (2 g.).

A suspension of the aldehydo-ester (2 g.) in methanol (40 ml.) was added in several portions, during 5 minutes, to concentrated hydrochloric acid (20 ml.) and water (10 ml.) containing amalgamated zinc (15 g.), and the mixture warmed gently for 5 minutes more, when the reaction with aqueous 2 : 4-dinitrophenylhydrazine sulphate was negative. The hot clear solution was decanted from the amalgam and combined with further alcohol washings of the reducing agent, and the total liquors diluted with water; the product rapidly separated as a crystalline solid. Purification from aqueous methanol gave *methyl 2 : 4-dihydroxy-6-methoxy-3-methylbenzoate* (1·6 g.) in rosettes of stout prisms, m. p. 202°, exhibiting a violet ferric reaction in alcohol (Found : C, 57·2; H, 6·2. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7%).

When a solution of the ester (1 g.) in water (7 ml.) containing potassium hydroxide (1 g.) was refluxed for 30 minutes in an atmosphere of nitrogen and the product isolated with ether, 2-methylphloroglucinol 5-methyl ether (0·65 g.) was obtained as an almost colourless crystalline mass, m. p. 124°. Robertson and Curd (*loc. cit.*) record m. p. 124°. The m. p. of a mixture with an authentic specimen of the isomeric 1-methyl ether was about 80°.

A solution of methyl 2 : 4-dihydroxy-6-methoxy-3-methylbenzoate (0·75 g.) in ether (100 ml.), containing zinc cyanide (0·5 g.) and hydrogen cyanide (5 ml.), was saturated with hydrogen chloride, and 24 hours later a solution in water (50 ml.) of the crystalline aldimine complex was hydrolysed on the steam-bath for 10 minutes. The crystalline aldehydo-ester separated from the cooled hydrolysate and was recrystallised from methyl alcohol giving *methyl 5-formyl-2 : 4-dihydroxy-6-methoxy-3-methylbenzoate* (0·6 g.) in long, slender prisms, m. p. 122°, giving a brown-violet ferric reaction in alcohol (Found : C, 55·7; H, 5·1. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in orange prisms, m. p. 262—263° (decomp.) (Found : N, 13·5. $C_{17}H_{16}O_9N_4$ requires N, 13·3%).

ω-Trichloro-4-hydroxy-2 : 6-dimethoxyacetophenone (VIII; R = $CO{\cdot}CCl_3$).—A solution of phloroglucinol dimethyl ether (5 g.) in ether (100 ml.) containing zinc chloride (5 g.) and trichloromethyl cyanide (10 g.) was saturated with hydrogen chloride at 5°, and a pale yellow crystalline solid separated. 24 Hours later the isolated complex was hydrolysed and crystallised from benzene giving *ω-trichloro-4-hydroxy-2 : 6-dimethoxyacetophenone* in pale yellow, massive prisms (3·7 g.), m. p. 117° (Found: C, 40·7; H, 3·4; Cl, 35·7. $C_{10}H_9O_4Cl_3$ requires C, 40·1; H, 3·0; Cl, 35·6%). Neither the purified nor the crude ketone gave a ferric reaction. Solution in warm 2N-sodium hydroxide rapidly gave a quantitative yield of 4-hydroxy-2 : 6-dimethoxybenzoic acid, m. p. 201° (decomp.) (Fischer and Pfeffer, *Annalen*, 1912, **389**, 211, record m. p. 175°) (Found: C, 54·4; H, 5·7. Calc. for $C_9H_{10}O_5$: C, 54·4; H, 5·1%).

A solution of the foregoing ketone (1 g.) in methanol was added to hydrochloric acid (5 ml.) and water (5 ml.) containing amalgamated zinc (5 g.). Reduction was completed at 50—60° in 5 minutes. Addition of water to the decanted reaction liquor gave rise to a quantitative yield of *1-ethylphloroglucinol 1 : 3-dimethyl ether*, which separated from aqueous methanol in glistening plates, m. p. 153° (Found: C, 65·9; H, 8·3. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%).

The same ethyl compound was produced when a mixture of the foregoing ω-trichloroacetophenone (0·6 g.), zinc dust (2 g.), and acetic acid (5 ml.) was heated under reflux for 30 minutes and the product isolated in the usual manner.

When zinc dust (2 g.) was added in small portions during 3 minutes to a solution of the previous ω-trichloroacetophenone (0·6 g.) in acetic acid (5 ml.) a violent reaction occurred. After being heated on the steam-bath for 2 minutes the product was isolated in the usual manner; purification from aqueous methanol gave a quantitative yield of 4-hydroxy-2 : 6-dimethoxyacetophenone, m. p. 185° (Canter, Curd, and Robertson, *loc. cit.*, record m. p. 185°).

ω-Trifluoro-4-hydroxy-2 : 6-dimethoxyacetophenone (VIII; R = $CO{\cdot}CF_3$).—A solution of phloroglucinol dimethyl ether (2·5 g.) in ether (50 ml.) containing zinc chloride (2 g.) was saturated at room temperature with hydrogen chloride, and trifluoromethyl cyanide (6 g.) was then introduced. 4 Hours later the yellow crystalline precipitate was collected and heated on the steam-bath during 15 minutes with water (50 ml.). The crystalline solid (1·5 g.) which separated from the cooled hydrolysate was steam-distilled; *ω-trifluoro-2-hydroxy-4 : 6-dimethoxyacetophenone* (0·2 g.) was collected and crystallised from aqueous methanol, forming bright yellow prisms, m. p. 87°, having an intense red-brown ferric reaction in alcohol (Found: C, 48·2; H, 4·2; F, 23·8. $C_{10}H_9O_4F_3$ requires C, 48·0; H, 3·6; F, 22·8%).

The non-volatile *ω-trifluoro-4-hydroxy-2 : 6-dimethoxyacetophenone* (1·0 g.) separated from aqueous methanol in almost colourless, long, slender needles, m. p. 155°, having a negative ferric reaction in alcohol (Found: C, 48·2; H, 4·1%).

ω-Trifluoro-2 : 6-dihydroxy-4-methoxy-3-methylacetophenone.—Prepared from a solution of 2-methylphloroglucinol 1-methyl ether (1·4 g.) in the usual manner, the *ketone* (0·5 g.) separated from benzene in bright yellow, massive prisms, m. p. 145°, unchanged by sublimation and having an intense violet-brown ferric reaction in alcohol (Found: C, 48·2; H, 4·0; F, 24·3. $C_{10}H_9O_4F_3$ requires C, 48·0; H, 3·6; F, 22·8%).

ω-Trifluoro-2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone.—Prepared from α-methylphloroglucinol 1 : 5-dimethyl ether (1·1 g.) and trifluoromethyl cyanide in the usual way, *ω-trifluoro-2-hydroxy-4 : 6-dimethoxy-3-methylacetophenone* (0·75 g.) separated from methanol in long, massive, rectangular, bright yellow prisms, m. p. 100°, having an intense green-brown ferric reaction in alcohol (Found: C, 49·9; H, 4·3. $C_{11}H_{11}O_4F_3$ requires C, 50·0; H, 4·2%). Sublimation at 100°/0·01 mm. gave the ketone in small squat intensely yellow prisms. Hydrolysis of this ketone with 4N-sodium hydroxide on the steam-bath during 10 minutes gave a quantitative yield of 2-hydroxy-4 : 6-dimethoxy-3-methylbenzoic acid, m. p. 182° (Curd and Robertson, *loc. cit.*, record m. p. 182°).

Methyl 2-Methylindole-3-carboxylate (XV; R = CO_2Me).—When a solution of 2-methyl-3-trichloroacetylindole (Fischer, *Ber.*, 1931, **64**, 2645) (0·5 g.) in methanol (17 ml.) containing aqueous 60% potassium hydroxide (1 drop) was refluxed for 5 minutes, and the solution cooled and diluted with water *methyl 2-methylindole-3-carboxylate* separated in quantitative yield, and was recrystallised from aqueous methanol in plate-like aggregates of needles, m. p. 165°, identical with the product obtained by the methylation of 2-methylindole-3-carboxylic acid with diazomethane (Found: N, 7·4. $C_{11}H_{11}O_2N$ requires N, 7·0%).

(With G. B. Sankey.) *2-Carbethoxy-4-hydroxy-3-methylcoumarone* (XIII; R = CO_2Et).—(*a*) The condensation of 2-acetylresorcinol (2·5 g.) and ethyl bromoacetate (2·0 g.) in boiling acetone (100 ml.) containing potassium carbonate (20 g.) was effected during 3 hours. Purification of the product from aqueous ethanol gave *ethyl (2-acetyl-3-hydroxyphenoxy)acetate* (2·9 g.) in almost colourless prisms, m. p. 74—75°, exhibiting a deep crimson ferric reaction in alcohol (Found: C, 60·9; H, 6·1. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%). Hydrolysis of this ester (1·0 g.) with 2N-sodium hydroxide (10 ml.) on the steam-bath during 30 minutes furnished (2-acetyl-3-hydroxyphenoxy)acetic acid which was not purified but cyclised directly by refluxing it during 80 minutes with sodium acetate (2·5 g.) and acetic anhydride (8 g.). The resultant solution was poured on ice (50 g.), and the oily coumarone acetate isolated with ether and hydrolysed on the steam-bath (1 hour) with 2N-sodium hydroxide. Acidification of the clear solution gave a brown granular solid which was purified from hot water, giving *4-hydroxy-3-methylcoumarone* (0·4 g.) in long, slender needles, m. p. 111°, having no ferric reaction in alcohol and dissolving in cold concentrated sulphuric acid to a red solution which became deep violet when warmed (Found: C, 72·5; H, 5·4. $C_9H_8O_2$ requires C, 73·0; H, 5·4%).

A solution of this coumarone (2·1 g.) in ether (100 ml.) containing zinc chloride (4·0 g.) and trichloromethyl cyanide (4 g.) was saturated with hydrogen chloride at 5°. 48 Hours later the semicrystalline ketimine complex was separated, dissolved in water (100 ml.), and hydrolysed on the steam-bath during 15 minutes, whereupon a pale green crystalline solid separated. Purification from light petroleum–

benzene gave *4-hydroxy-3-methyl-2-trichloroacetylcoumarone* (1·7 g.) in rosettes of bright green prisms, m. p. 159°, giving no ferric reaction in alcohol (Found: C, 45·6; H, 2·5. $C_{11}H_7O_3Cl_3$ requires C, 45·1; H, 2·4%).

When a solution of the ketone (1·2 g.) in ethanol (15 ml.) containing 2 drops of 60% potassium hydroxide was refluxed for 5 minutes and the product isolated in the normal way, *2-carbethoxy-4-hydroxy-3-methylcoumarone* separated from aqueous ethanol in slender prisms, m. p. 155°, identical with the product obtained by method (*b*) (Found: C, 66·0; H, 5·9. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). This compound gives no ferric reaction in alcohol and dissolves in cold concentrated sulphuric acid to a pale yellow solution which becomes deep violet on being warmed.

(*b*) A solution of ethyl (2-acetyl-3-hydroxyphenoxy)acetate (2 g.) in ethanol (15 ml.) containing sodium ethoxide (from 0·2 g. of sodium) was refluxed for 1 hour. After dilution with water (100 ml.) and acidification with hydrochloric acid, the buff precipitate was extracted with 2N-sodium hydrogen carbonate and purified from light petroleum–benzene giving 2-carbethoxy-4-hydroxy-3-methylcoumarone (0·2 g.), m. p. 155°, identical in every way with the product from method (*a*).

The 2 : 4-*dinitrophenylhydrazone* of ω-trifluoro-2 : 4-dimethoxyacetophenone separated during 1 week at room temperature and crystallised from alcohol in rosettes of orange needles, m. p. 195° (Found: N, 13·3. $C_{18}H_{15}O_6N_4F_3$ requires N, 13·5%).

Prepared similarly the 2 : 4-*dinitrophenylhydrazone* of 6-methoxy-2-trifluoroacetylcoumarone formed blood-red prisms, m. p. 190—191° (decomp.), from alcohol (Found: N, 12·5. $C_{18}H_{13}O_6N_4F_3$ requires N, 12·8%).

The author thanks Dr. D. H. Johnson for the preparation of the trichloromethyl cyanide and Imperial Chemical Industries Limited, General Chemicals Division, for a generous gift of trifluoroacetic acid.

UNIVERSITY OF LIVERPOOL. [*Received, July 6th*, 1951.]

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713. *Organic Fluoro-compounds. Part VI.* Some Trifluoromethyl-chromones and -coumarins.*

By W. B. WHALLEY.

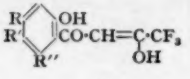
The condensation of ethyl trifluoroacetate with *o*-hydroxyacetophenones proceeds normally, to furnish *o*-hydroxy-diketones of type (I), which are cyclised by mineral acid to the corresponding 2-trifluoromethylchromones (II). Condensation of the appropriate phenols with ethyl trifluoroacetoacetate readily gives the isomeric 4-trifluoromethylcoumarins (III), except in the case of phloroglucinol, which furnishes the α-pyrono-coumarin (VI), whilst 3 : 5-dihydroxybenzotrifluoride and ethyl acetoacetate yield a mixture of 5-hydroxy-4-methyl-7-trifluoromethyl- (X; R = H) and 7-hydroxy-4-methyl-5-trifluoromethyl-coumarin (IX; R = H). The preparation of 3-trifluoroacetylcoumarins of type (IV) from *o*-hydroxy-aldehydes and ethyl trifluoroacetate does not proceed easily.

WITH the object of exploring the potentialities of suitable substances containing the trifluoromethyl and trifluoroacetyl groups as intermediates for the preparation of difficultly accessible fluorine-free oxygen-heterocylic compounds, the preparation and properties of several ω-trifluoroacetylacetones and trifluoromethyl-chromones and -coumarins have been investigated.

Condensation of 2-aceto-*p*-cresol (OH = 1), 2-hydroxy-4 : 6-dimethylacetophenone, and 2-hydroxy-4-methoxyacetophenone with ethyl trifluoroacetate proceeded normally under the influence of powdered sodium with the production of the corresponding diketones (I), which very easily suffer fission by alkali with the regeneration of the parent acetophenones. The diketones cyclised readily in boiling alcohol containing hydrochloric acid to furnish the corresponding chromones (II), and gave rise to monoximes; these oximes are presumably represented by structures of type (V) because by analogy with the ω-trifluoroacetophenones (Part IV, *J.*, 1951, 665) the carbonyl group adjacent to the trifluoromethyl group will be comparatively unreactive towards carbonyl reagents, owing to enolisation. In contrast with the ω-trifluorohydroxy- and ω-trichlorohydroxy-acetophenones (Part IV, *loc. cit.*, and Part V, preceding paper), these hydroxy-diketones are colourless; this is in accord with general considerations which indicate that the electrophilic properties of the ω-fluoro atoms can be

* Part V, preceding paper.

exerted by the production of the enol (I), and thus the quinonoid structure which causes colour in the acetophenones is not invoked (cf. preceding paper).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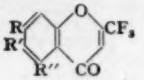
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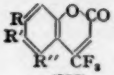
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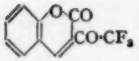
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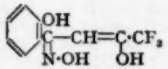
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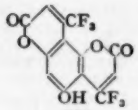
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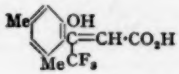
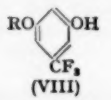
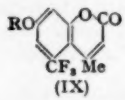

(VII)

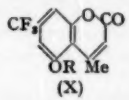
By the Pechmann condensation (*Ber.*, 1883, **16**, 2119) with ethyl trifluoroacetoacetate, *p*-cresol, 3 : 5 : 1-xylenol, resorcinol, and resorcinol monomethyl ether gave the corresponding 4-trifluoromethylcoumarins (III) in excellent yield, the structure of which is clearly indicated by the products' not being identical with the chromones obtained by the unequivocal method recorded above. However, condensation of phloroglucinol with ethyl trifluoroacetoacetate gave a compound which appeared to consist entirely of one of the possible isomeric forms of the α-pyrono-coumarin type (VI) : it is of interest that phloroglucinol and ethyl acetoacetate furnish the expected 5 : 7-dihydroxy-4-methylcoumarin (Pechmann and Cohen, *Ber.*, 1884, **17**, 2189). Theoretical considerations indicate that the 4-trifluoromethyl group in these coumarins should be of great stability, and this has been confirmed by the failure to produce the corresponding coumarin-4-carboxylic acid by a variety of hydrolytic methods.

When solutions of 6-methyl-4-trifluoromethylcoumarin (III; R′ = R″ = H, R′ = Me) and 7-methoxy-4-trifluoromethylcoumarin (III; R = R″ = H, R = OMe) in 2N-sodium hydroxide were acidified, the parent coumarin was isolated. However, 5 : 7-dimethyl-4-trifluoromethylcoumarin (III; R′ = H, R = R″ = Me) gave under these conditions the corresponding cinnamic acid (VII), which exhibited considerable stability and was converted into the parent coumarin only by evaporation above the melting point. This behaviour of *cis-o*-hydroxycinnamic acids has been noted in very few cases and only where negative substituents are present (*e.g.*, Miller and Kinkelin, *Ber.*, 1889, **22**, 1706; Jordan and Thorpe, *J.*, 1915, 387); it is presumably to be ascribed in this instance to the influence of the strongly electrophilic trifluoromethyl group.

Application of the Pechmann condensation with ethyl acetoacetate to 3 : 5-dihydroxybenzotrifluoride (VIII; R = H) (Part I, *J.*, 1949, 3016) gave, as might be expected, a mixture of the isomeric coumarins (IX and X; R = H). The structures of these two substances were not rigorously established but are based on the production of a yellow solution by one coumarin in 2N-sodium hydroxide, and the absence of such a coloration in the case of the second; production of this colour is a well-known characteristic reaction of 5-hydroxycoumarins (Collie


(VIII)


(IX)


(X)

and Chrystall, *J.*, 1907, **91**, 1804; Dey, *J.*, 1915, **107**, 1614, 1621) and hence the coumarin which responds positively to this test is allotted the structure (X; R = H). Methylation by potassium carbonate–methyl iodide readily furnished the corresponding methyl ethers (IX and X; R = Me). Condensation of 3-hydroxy-5-methoxybenzotrifluoride (VIII; R = Me) (Part I, *loc. cit.*) yielded a small quantity of a mixture from which only 7-methoxy-4-methyl-5-trifluoromethylcoumarin could be isolated in a state of purity.

Demethylation of 3-hydroxy-5-methoxybenzotrifluoride (VIII; R = Me), which is now readily available (Robertson, Whalley, and Yates, *J.*, 1951, 2013), provides a much improved route to 3 : 5-dihydroxybenzotrifluoride.

3-Trifluoroacetylcoumarins of type (IV) could not be obtained from ethyl trifluoroacetoacetate and the appropriate *o*-hydroxy-aldehydes; condensation did not proceed easily at room temperature under normal conditions, and application of heat gave rise to dark red resins.

Experimental.

6-Methyl-2-trifluoromethylchromone (II; R = R″ = H, R′ = Me).—A mixture of 2-hydroxy-5-methylacetophenone (5 g.), ethyl trifluoroacetate (17 ml.), and powdered sodium (2 g.) was heated on the steam-bath during 1 hour. The semi-solid yellow mixture was decomposed by the careful addition of ice-water (100 ml.), well shaken to homogenise the product, and acidified with acetic acid, and the semi-crystalline precipitate collected and purified from aqueous methanol, giving *2-hydroxy-5-methyl-ω-trifluoroacetoacetophenone* (3 g.) as colourless, slender prisms or, from benzene–light petroleum as rosettes of glistening, colourless needles, m. p. 157° (Found: C, 53·6; H, 3·4; F, 22·1. $C_{11}H_9O_3F_3$ requires C, 53·7; H, 3·7; F, 23·2%). The product is readily soluble in methyl alcohol, ethyl alcohol, acetone, and ether, moderately soluble in benzene, and sparingly soluble in light petroleum, and exhibits a weak green-brown ferric reaction in alcohol. The *oxime* prepared by the sodium acetate method separated from aqueous methanol in colourless needles, m. p. 140° (Found: C, 49·9; H, 3·9; N, 4·9. $C_{11}H_{10}O_3NF_3$ requires C, 50·5; H, 4·0; N, 5·4%).

When a solution of the diketone in 2N-sodium hydroxide was kept at room temperature for 6 hours and acidified, 2-hydroxy-5-methylacetophenone was precipitated in quantitative yield.

A solution of the foregoing diketone (0·5 g.) in ethanol (5 ml.) containing concentrated hydrochloric acid (3 drops) was heated under reflux during 3 minutes, cooled, and diluted with water. The oil initially precipitated rapidly crystallised, and was purified from aqueous methanol, giving *6-methyl-2-trifluoromethylchromone*, m. p. 53°, in quantitative yield (Found: C, 57·2; H, 3·4. $C_{11}H_7O_2F_3$ requires C, 57·9; H, 3·1%). The chromone was easily soluble in alcohol, ether, acetone, benzene, and light petroleum, and gave no ferric reaction in alcohol.

7-Methoxy-2-trifluoromethylchromone (II; R = OMe, R′ = R″ = H).—When a solution of 2-hydroxy-4-methoxyacetophenone (5 g.) in ethyl trifluoroacetate (20 ml.) containing powdered sodium (2 g.) was heated on the steam-bath during 1½ hours, and the product isolated as previously described, *2-hydroxy-4-methoxy-ω-trifluoroacetoacetophenone* (3·5 g.) separated from benzene in rosettes of colourless, long, slender needles, m. p. 136°, which changed to colourless, massive prisms, m. p. 136°, on prolonged contact with the solution (Found: C, 50·8; H, 3·4; F, 22·0. $C_{11}H_9O_4F_3$ requires C, 50·4; H, 3·4; F, 21·7%). The solution in alcohol gave a weak red-brown ferric reaction.

A solution of the diketone (0·2 g.) in 2N-sodium hydroxide (5 ml.) was kept at room temperature during 6 hours and then acidified; pæonol (0·15 g.) was precipitated. Prepared by the sodium acetate method, the *oxime* separated from aqueous methanol in colourless plates, m. p. 125° (Found: C, 45·2; H, 4·1; N, 4·8. $C_{11}H_{10}O_4NF_3,H_2O$ requires C, 45·4; H, 4·1; N, 4·8%).

Cyclisation of the diketone in boiling alcohol containing 3 drops of concentrated hydrochloric acid during 5 minutes gave *7-methoxy-2-trifluoromethylchromone* in quantitative yield. From aqueous methyl alcohol it formed colourless, long, slender prisms, m. p. 110°, insoluble in cold 2N-sodium hydroxide and giving a negative ferric reaction in alcohol (Found: C, 53·7; H, 3·0; F, 23·6. $C_{11}H_7O_3F_3$ requires C, 54·1; H, 2·9; F, 23·3%).

5 : 7-*Dimethyl-2-trifluoromethylchromone* (II; R = R″ = Me, R′ = H).—Prepared from 2-hydroxy-4 : 6-dimethylacetophenone (5 g.), ethyl trifluoroacetate (20 ml.), and powdered sodium (2 g.) in the usual way, *2-hydroxy-4 : 6-dimethyl-ω-trifluoroacetoacetophenone* separated from aqueous methanol or benzene in colourless prisms (3 g.), m. p. 137°, readily soluble in 2N-sodium hydroxide and exhibiting a weak green-brown ferric reaction in alcohol (Found: C, 55·4; H, 4·4; F, 21·9. $C_{12}H_{11}O_3F_3$ requires C, 55·4; H, 4·2; F, 21·9%). The diketone was hydrolysed quantitatively to 2-hydroxy-4 : 6-dimethylacetophenone during 6 hours when dissolved in 2N-sodium hydroxide. The *oxime*, prepared by the sodium acetate method, separated from aqueous methanol in clusters of colourless prisms, m. p. 138° (Found: C, 52·2; H, 4·5; N, 4·2. $C_{12}H_{12}O_3NF_3$ requires C, 52·4; H, 4·4; N, 5·1%).

Prepared in almost quantitative yield by the cyclisation of the foregoing diketone in boiling alcohol containing 3 drops of concentrated hydrochloric acid 5 : 7-*dimethyl-2-trifluoromethylchromone* separated from aqueous methanol in colourless shimmering, long, flat prisms, m. p. 105° (Found: C, 59·4; H, 3·8; F, 23·4. $C_{12}H_9O_2F_3$ requires C, 59·5; H, 3·7; F, 23·5%). The chromone was insoluble in cold 2N-sodium hydroxide and gave a negative ferric reaction in alcohol.

6-Methyl-4-trifluoromethylcoumarin (III; R = R″ = H, R′ = Me).—*p*-Cresol (3 g.) and ethyl trifluoroacetoacetate (6 g.) were dissolved in concentrated sulphuric acid (10 ml.) and 2 days later the solution was poured on crushed ice. The colourless precipitate crystallised from methanol, to furnish *6-methyl-4-trifluoromethylcoumarin* in long, slender, glistening, colourless prisms (2 g.), m. p. 111° (Found: C, 57·9; H, 3·1; F, 25·4. $C_{11}H_7O_2F_3$ requires C, 57·9; H, 3·1; F, 25·0%). When a suspension of this coumarin was warmed on the steam-bath with 2N-sodium hydroxide, dissolution occurred during 20 minutes; careful acidification (Congo-red) with 2N-hydrochloric acid then precipitated the coumarin, identified by m. p. and mixed m. p.

7-Methoxy-4-trifluoromethylcoumarin (III; R = OMe, R′ = R″ = H).—(*a*) Prepared from resorcinol (2 g.), ethyl trifluoroacetoacetate (5 g.), and concentrated sulphuric acid (5 ml.) during 2 days in the usual way, *7-hydroxy-4-trifluoromethylcoumarin* separated from methanol in colourless, glistening plates (1·6 g.), m. p. 178°, easily soluble in cold 2N-sodium hydroxide and exhibiting a negative ferric reaction in alcohol (Found: C, 52·3; H, 2·1; F, 24·3. $C_{10}H_5O_3F_3$ requires C, 52·2; H, 2·2; F, 24·8%). Methylation of the foregoing coumarin in boiling acetone by potassium carbonate–methyl iodide during 3 hours gave *7-methoxy-4-trifluoromethylcoumarin* which separated from aqueous methanol in clusters of colourless needles, m. p. 112°, unchanged by sublimation at 120°/0·1 mm. (Found: C, 53·7; H, 3·2. $C_{11}H_7O_3F_3$ requires C, 54·1; H, 2·9%).

(*b*) Resorcinol monomethyl ether (0·5 g.) and ethyl trifluoroacetoacetate (1 g.) were dissolved in concentrated sulphuric acid (5 ml.) and 2 days later the solution was poured on ice. The product

(0·5 g.) which separated from aqueous methanol in clusters of colourless needles was identical with that prepared by method (*a*).

A suspension of this coumarin in 2N-sodium hydroxide was warmed on the steam-bath during 30 minutes, and the clear solution cooled and acidified, giving rise to the parent coumarin.

5 : 7-*Dimethyl-4-trifluoromethylcoumarin* (III; R = R'' = Me, R' = H).—Prepared from 3 : 5 : 1-xylenol (3 g.), ethyl trifluoroacetoacetate (6 g.), and concentrated sulphuric acid (10 ml.) during 2 days, 5 : 7-*dimethyl-4-trifluoromethylcoumarin* separated from methanol in massive, colourless, glistening prisms (4 g.), m. p. 99° (Found: C, 59·6; H, 3·7; F, 23·9. $C_{12}H_9O_2F_3$ requires C, 59·5; H, 3·7; F, 23·5%). The mixed m. p. with 5 : 7-dimethyl-2-trifluoromethylchromone was about 75°. The coumarin dissolved during 30 minutes on the steam-bath in 2N-sodium hydroxide, and after acidification the precipitated *cinnamic acid* was crystallised from benzene–light petroleum as colourless, rectangular plates, m. p. 149°, easily soluble in 2N-sodium hydrogen carbonate solution (Found: C, 55·2; H, 4·4. $C_{12}H_{11}O_2F_3$ requires C, 55·4; H, 4·2%). Sublimation at 160°/0·1 mm. regenerated the parent coumarin (m. p. and mixed m. p.).

Condensation of Phloroglucinol with Ethyl Trifluoroacetoacetate.—Prepared from phloroglucinol (2 g.) and ethyl trifluoroacetoacetate (4 g.) in concentrated sulphuric acid (10 ml.) during 2 days, *5-hydroxy-4 : 4'-bistrifluoromethyl-2'-pyrono*(6' : 5'-7 : 8)*coumarin*(?) (VI) separated from methanol in very pale yellow, stout prisms (1·2 g.), m. p. 299—300° (Found: C, 45·1; H, 1·4; F, 30·2. $C_{14}H_4O_5F_6$ requires C, 45·9; H, 1·1; F, 31·2%).

3 : 5-*Dihydroxybenzotrifluoride.*—A mixture of 3-hydroxy-5-methoxybenzotrifluoride (15 g.) and hydriodic acid (100 ml.; *d* 1·7) was refluxed for 20 hours, diluted with water (125 ml.), and steam-distilled to remove a trace of starting material. The cooled reaction mixture was extracted with ether (5 × 100 ml.), and the extract washed with 2N-sodium hydrogen carbonate, dilute sodium bisulphite solution, and water, dried, and distilled, to give 3 : 5-dihydroxybenzotrifluoride (12·5 g.), b. p. 104°/3 mm., identical with a specimen prepared by an alternative method (Part I, *loc. cit.*).

7-*Methoxy-4-methyl-5-trifluoromethylcoumarin.*—(*a*) A solution of 3 : 5-dihydroxybenzotrifluoride (5 g.) and ethyl acetoacetate (5 g.) in concentrated sulphuric acid (10 ml.) was kept at room temperature for 5 days, and the resultant golden-yellow solution poured on crushed ice (50 g.). The dried colourless, crystalline precipitate (3·5 g.) was fractionally crystallised from ethyl acetate. The first, sparingly soluble fraction (*ca.* 1 g.) separated from ethyl acetate in stout colourless needles of *7-hydroxy-4-methyl-5-trifluoromethylcoumarin*, m. p. 273° (Found: C, 54·3; H, 3·2. $C_{11}H_7O_3F_3$ requires C, 54·1; H, 2·9%). The substance was very readily soluble in methanol and ethanol with a blue fluorescence, gave no ferric reaction in alcohol, and dissolved in cold 2N-sodium hydroxide to furnish a colourless solution. Methylation of this coumarin in boiling acetone during 1 hour by methyl iodide–potassium carbonate gave a quantitative yield of *7-methoxy-4-methyl-5-trifluoromethylcoumarin* which separated from methanol in long, slender, colourless prisms, m. p. 192° (Found: C, 55·4; H, 3·3; F, 21·7. $C_{12}H_9O_3F_3$ requires C, 55·8; H, 3·5; F, 22·1%).

The mother-liquors from the fractional crystallisation were evaporated to dryness and repeatedly extracted with hot benzene. Concentration of this benzene extract gave rise to *5-hydroxy-4-methyl-7-trifluoromethylcoumarin* (*ca.* 1 g.) which separated from benzene or aqueous methanol in colourless plates, m. p. 251° (Found: C, 54·3; H, 3·4. $C_{11}H_7O_3F_3$ requires C, 54·1; H, 2·9%). The substance gives no ferric reaction in alcohol, is readily soluble in hot benzene, and dissolves in cold 2N-sodium hydroxide to give a bright yellow solution. The alcoholic solution exhibits a faint blue fluorescence. Methylation by the methyl iodide–potassium carbonate method during 1 hour gave a quantitative yield of 5-methoxy-4-methyl-7-trifluoromethylcoumarin which separated from aqueous methanol in colourless needles, m. p. 147° (mixed m. p. with the isomeric coumarin was about 135°) (Found: C, 55·4; H, 3·3; F, 21·7. $C_{12}H_9O_3F_3$ requires C, 55·8; H, 3·5; F, 22·1%).

(*b*) A solution of 3-hydroxy-5-methoxybenzotrifluoride (5 g.) and ethyl acetoacetate (5 g.) in concentrated sulphuric acid was kept at room temperature for 3 days and after isolation the colourless precipitate (1 g.) was fractionally crystallised from aqueous methanol to give a small quantity (*ca.* 0·2 g.) of *7-methoxy-4-methyl-5-trifluoromethylcoumarin*, m. p. 192°, identical with a specimen prepared by method (*a*).

The author thanks Imperial Chemical Industries Limited, General Chemicals Division, for a generous gift of trifluoroacetic acid.

UNIVERSITY OF LIVERPOOL. [*Received, July 6th,* 1951.]

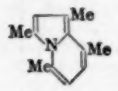
714. *Condensations of 2 : 4-Dimethylpyrrole.*

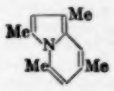
By J. E. Saxton.

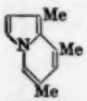
The condensation of 2 : 4-dimethylpyrrole with acetonylacetone and its equivalent self-condensation under the influence of zinc acetate in acetic acid have been re-examined. The products have been shown to be 1 : 3 : 5 : 8- and 1 : 3 : 5 : 7-tetramethylpyrrocoline, respectively.

The condensation of 2 : 4-dimethylpyrrole with acetonylacetone and its self-condensation under the influence of zinc acetate in acetic acid were studied by Plancher (*Ber.*, 1902, **35**, 2606; *Atti R. Accad. Lincei*, 1902, (v), **11**, ii, 210; Plancher and Ciusa, *ibid.*, 1906, (v), **15**, ii, 453), who obtained a base, $C_{12}H_{15}N$, from each reaction. Plancher initially regarded the product from the former condensation as a bridged-ring compound containing a secondary nitrogen atom, but later preferred a tetramethylindolenine structure. This second postulate provided a closer analogy with the self-condensation of 2-methylpyrrole to 2 : 4-dimethylindole, and with the condensation of pyrrole and acetonylacetone with the formation of 4 : 7-dimethylindole.

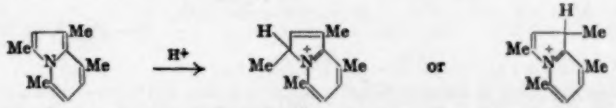
Similarly for the self-condensation of 2 : 4-dimethylpyrrole Plancher assumed partial hydrolysis to α-methyl-lævulic aldehyde, followed by condensation with dimethylpyrrole to give either another bridged-ring compound or a tetramethylindolenine. The condensation of skatole and acetonylacetone to give 1 : 5 : 8-trimethyl-2 : 3-benzopyrrocoline led Sir Robert Robinson and the present author to expect that the above-mentioned compounds would be found to be pyrrocolines (*J.*, 1950, 3136). This expectation has now been verified, and the compounds have been shown to be 1 : 3 : 5 : 8-tetramethylpyrrocoline (I) and 1 : 3 : 5 : 7-tetramethylpyrrocoline (II), respectively.


(I)


(II)


(III)

The condensation of 2 : 4-dimethylpyrrole with acetonylacetone was carried out according to the conditions described by Plancher, using zinc acetate in acetic acid for 24 hours at 118°, but a more convenient preparative method was found in the use of ethanolic hydrogen chloride for 15—20 minutes at 0°. The product had the properties of a substituted pyrrocoline: the base did not dissolve in cold dilute acid, but did so when warmed, and neither cooling nor dilution precipitated the base. In light petroleum or ethanol solution the base exhibited a blue fluorescence, and indeed the fluorescent properties of the base were visible in the crystalline solid. Addition of acid to the alcoholic solution destroyed the fluorescence, owing to fixation of the structure in the pyridinoid form:

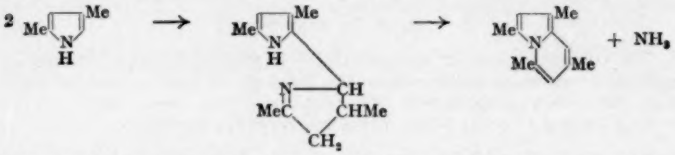


The base gives only a faint pine-shaving reaction, and does not give a coloured melt with anhydrous oxalic acid. It does not give an Ehrlich reaction or the ordinary pyrrole reactions with isatin or phenanthraquinone.

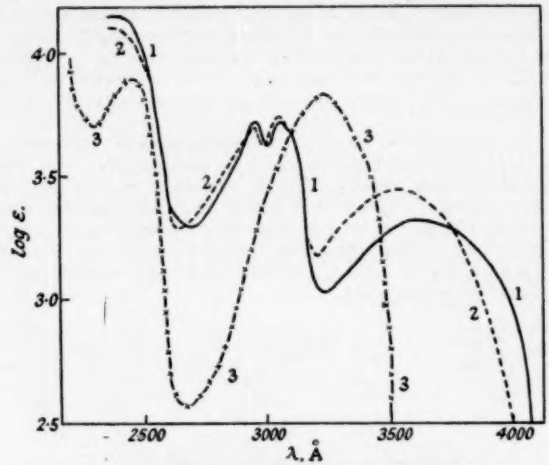
Reduction of the base was easily effected in ethanol, Raney nickel catalyst being used at elevated temperature and pressure, to give a strong tertiary base, $C_{12}H_{23}N$, which gave no reaction with nitrous acid in the cold or with acetic anhydride. Hence Plancher's formulations cannot be entertained, and the product must be 1 : 3 : 5 : 8-tetramethylpyrrocoline.

The self-condensation of 2 : 4-dimethylpyrrole gave a base isomeric with (I) and very similar in its chemical behaviour and characteristic ultra-violet absorption. There are two possible formulæ for this product, namely, (II) and (III). Of these, the former is to be preferred, if it may be assumed that the condensation proceeds *via* the initial formation of a dipyrrole,

as occurs in the formation of indoles from pyrroles (Allen, Gilbert, and Young, *J. Org. Chem.*, 1937, **2**, 235):

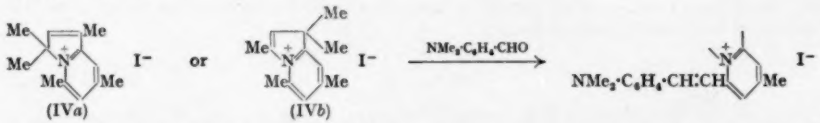


The methiodide of this base (assumed to be II) has the formula (IV*a* or *b*), the molecule containing a true pyridine ring, bearing methyl groups *ortho* and *para* to the nitrogen atom. These methyl



1. 1 : 3 : 5 : 7-*Tetramethylpyrrocoline in ethanol solution.*
2. 1 : 3 : 5 : 8-*Tetramethylpyrrocoline in ethanol solution.*
3. 1 : 3 : 5 : 8-*Tetramethylpyrrocoline in* 0·05N-*ethanolic hydrochloric acid.*

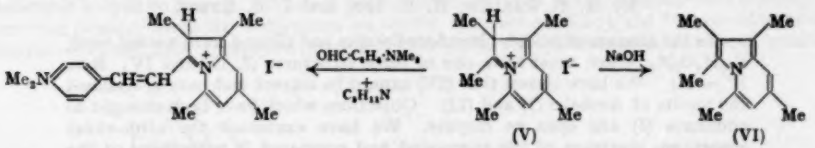
groups should therefore be active, and should condense with aldehydes under the influence of a base. However, there is so far no adequate evidence which can lead to the differentiation of (IV*a*) and (IV*b*):



The entering methyl group is assumed to enter either position 1 or 3 (most probably position 3, as in IV*a*), since these are the sites of attack by electrophilic substituents (Borrows, Holland, and Kenyon, *J.*, 1946, 1069 *et seq.*; 1947, 670, 672; Coulson and Longuet-Higgins, *Trans. Faraday Soc.*, 1947, **43**, 87). On the other hand, the methiodide from (III) has two methyl groups *meta* to the nitrogen atom, which are consequently inert.

It should be noted that there is a third formula possible for this methiodide (V), which could also condense with *p*-dimethylaminobenzaldehyde as indicated. However, this formulation is eliminated by the following evidence: if the methiodide has the formula (V), then solution of the substance in water followed by basification should lead to a pyrrocoline base (VI), *i.e.*, the original base with a methyl group in position 2. This type of reaction is not possible with (IV). The base could easily be recognised in solution by the characteristic pyrrocoline fluorescence; this simple experiment showed conclusively that no trace of a pyrrocoline base was obtained on basification, and no ether-soluble material was produced.

Condensation of the methiodide of the pyrrocoline base with *p*-dimethylaminobenzaldehyde in ethanol solution in the presence of piperidine rapidly gave a deep red cyanine dye, thus proving that the product of the self-condensation of 2 : 4-dimethylpyrrole is 1 : 3 : 5 : 7-tetramethylpyrrocoline.



(V) (VI)

The ultra-violet absorption curves of these two pyrrocolines are given in the figure. They show a marked resemblance to the curves for the 2 : 3-benzopyrrocolines (Robinson and Saxton, *loc. cit.*) although absorption does not extend into the visible region. In acid solution, the absorption is entirely different, and the curve is characteristic of a pyridine derivative.

Experimental.

(Analyses are by Drs. G. Weiler and F. B. Strauss, and absorption spectra by Dr. Strauss.)

1 : 3 : 5 : 8-*Tetramethylpyrrocoline* (I) (cf. Plancher, *Atti R. Accad. Lincei*, 1902, (v), **11**, ii, 213).—(*a*) 2 : 4-Dimethylpyrrole (5 g.), acetonylacetone (7·5 g.), and zinc acetate (7·5 g.) were heated under reflux in 90% acetic acid (250 ml.) for 24 hours. The solvent was removed *in vacuo*, the residue made alkaline, and the product distilled in steam. The solid was collected and crystallised from ethanol. 1 : 3 : 5 : 8-Tetramethylpyrrocoline was obtained as long prisms, m. p. 135°.

(*b*) A solution of 2 : 4-dimethylpyrrole (5 g.) and acetonylacetone (7·5 g.) in ethanol (25 ml.) was cooled in ice, and dry hydrogen chloride passed in until a portion of the solution gave no colour with Ehrlich's reagent (approx. 15—20 minutes). The solution was then made alkaline and distilled in steam. The solid was collected and crystallised from ethanol. 1 : 3 : 5 : 8-Tetramethylpyrrocoline (2 g.) was obtained as long prisms, m. p. 135° [Found: C, 83·2; H, 8·5; N, 8·0%; *M* (cryoscopic in camphor), 170. Calc. for $C_{12}H_{15}N$: C, 83·3; H, 8·7; N, 8·1%; *M*, 173].

Solutions of the base in ethanol or light petroleum exhibit a marked blue fluorescence. Addition of acid to the ethanolic solution destroys the fluorescence. As reported by Plancher, the base does not give pyrrole reactions, nor does it combine with methyl iodide in the cold.

Octahydro-1 : 3 : 5 : 8-*tetramethylpyrrocoline*.—1 : 3 : 5 : 8-Tetramethylpyrrocoline (1·5 g.) was reduced in ethanol solution, Raney nickel catalyst being used, with hydrogen at 80 atm. pressure at 100°. The product was isolated by distillation, and *octahydro*-1 : 3 : 5 : 8-*tetramethylpyrrocoline* (1·0 g.) obtained as a colourless oil, b. p. 86—87°/8 mm. (Found: C, 79·5; H, 12·8; N, 7·5. $C_{12}H_{23}N$ requires C, 79·6; H, 12·7; N, 7·7%).

The *picrate* crystallised from ethanol as yellow rhombs, m. p. 172—177° (Found: C, 53·1; H, 6·2; N, 13·5, 13·6. $C_{18}H_{22}N,C_6H_3O_7N_3$ requires C, 52·7; H, 6·3; N, 13·6%).

Octahydro-1 : 3 : 5 : 8-tetramethylpyrrocoline was a strong tertiary base which showed no reaction with nitrous acid in the cold or with acetic anhydride.

1 : 3 : 5 : 7-*Tetramethylpyrrocoline* (II) (cf. Plancher, *Ber.*, 1902, **35**, 2606).—A mixture of 2 : 4-dimethylpyrrole (5 g.), zinc acetate (22·5 g.), and acetic acid (150 ml.) was heated under reflux for 24 hours. The solvent was removed *in vacuo*, and the product, after being made strongly alkaline, was distilled in steam. The solid was collected from the distillate and crystallised from methanol, being obtained as prisms, m. p. 74—75°, which soon develop a delicate green tinge when kept in air. Plancher (*loc. cit.*) reports m. p. 74° and the same property (Found: C, 82·8; H, 8·6. Calc. for $C_{12}H_{15}N$: C, 83·3; H, 8·7%).

The base closely resembled the tetramethylpyrrocoline described above, showing a blue fluorescence in light petroleum solution and a blue-green fluorescence in ethanol. Addition of acid to the alcoholic solution destroyed the fluorescence.

1 : 3 : 5 : 7-*Tetramethylpyrrocoline methiodide* was prepared by heating a solution of the free base in methyl iodide for an hour at 100° in a sealed tube, and was obtained from ethanol or water as rhombs, m. p. 245—248° (Found: C, 49·9; H, 5·7; I, 40·4. $C_{13}H_{18}N,CH_3I$ requires C, 49·5; H, 5·7; I, 40·3%).

This methiodide (0·5 g.) was heated under reflux in ethanol solution for 2 hours with *p*-dimethylaminobenzaldehyde (0·2 g.) and piperidine (2 drops). An intense red colour developed, indicating formation of the dye, which was precipitated in an amorphous state by the addition of ether. Unfortunately it could not be obtained crystalline.

The methiodide (50 mg.) was dissolved in water (2·5 ml.) and excess of sodium hydroxide added. No turbidity was produced, and the solution remained colourless and non-fluorescent. The solution was then warmed for a few minutes, cooled, and extracted with ether. The whole of the material remained in the aqueous layer, which was still colourless and non-fluorescent.

The author is indebted to Prof. Sir Robert Robinson, O.M., F.R.S., for his interest in the work, which was carried out during the tenure of a D.S.I.R. Maintenance Grant. This acknowledgment to the D.S.I.R. also applies to an earlier paper (*J.*, 1950, 3136).

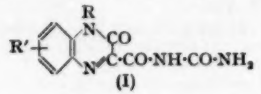
Dyson Perrins Laboratory, Oxford University. [*Received, July 10th*, 1951.]

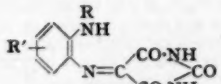
715. *The Structure of the Product formed from Alloxan and o-Phenylenediamine in the Absence of Acid.*

By R. B. Barlow, H. R. Ing, and I. M. Lewis.

In the absence of acid, *o*-phenylenediamine and alloxan form a compound, $C_{10}H_8O_3N_4$, which must have one of three structures (I, II, and IV; R = R′ = H). We have shown that (IV) cannot be correct and have re-assessed the merits of formulæ (I) and (II). Objections which have been thought to eliminate (I) are open to dispute. We have examined the ultra-violet absorption spectrum of the compound and compared it with those of the dihydroketoquinoxalinecarboxylic acid (III; R = R′ = H) and the compound formed from 4 : 5-dichloro-2-dimethylaminoaniline and alloxan; we conclude that (I) is almost certainly the correct formula.

The reactions of tolylenediamine and of *o*-phenylenediamine with alloxan in water were reported by Hinsberg (*Ber.*, 1885, **18**, 1228; *Annalen*, 1896, **292**, 247) to produce the dihydroketoquinoxalinecarboxyureides (I; R = H). When similar experiments were performed with *N*-monosubstituted *o*-phenylenediamines in methanol (Kühling, *Ber.*, 1893, **26**, 540; Kühling and Kaselitz, *Ber.*, 1906, **39**, 1314), in a mixture of ethanol, water, and acetic acid (Kuhn, Weygand, and Rudy, *Ber.*, 1935, **68**, 633), and in pyridine (Tishler, Wellman, and Ladenburg, *J. Amer. Chem. Soc.*, 1945, **67**, 2165), the products were formulated as the anils (II). All the compounds are easily hydrolysed to the dihydroketoquinoxalinecarboxylic acids (III) by alkali, and it is possible that they are actually all of the same type (Rudy and Cramer, *Ber.*, 1938, **71**, 1234). A third type of structure, which does not appear to have been considered before, is the *spiro*-arrangement (IV); this was eliminated in the following way.


(I)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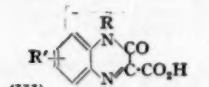
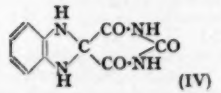

(III)

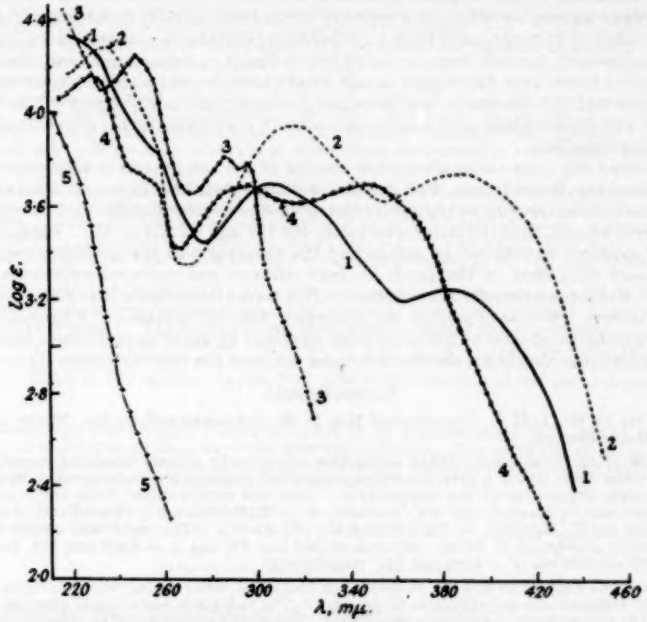

(IV)

The product of the reaction between *o*-phenylenediamine and alloxan, which was the same whether the solvent was water or methanol, was reduced with hydrogen at room temperature and atmospheric pressure with Raney nickel catalyst suspended in methanol. The uptake of hydrogen corresponded to the addition of two hydrogen atoms, and the product was identical with that obtained from the reaction of *o*-phenylenediamine with dialuric acid in methanol. In addition to mixed m. p. tests, a check was provided by the ultra-violet absorption spectra, which were identical. This result rules out the *spiro*-structure (IV) and leaves only structures (I) and (II).

The compound (I or II; R = R′ = H) has none of the properties associated with a free amino-group: (i) it is not basic and dissolves appreciably only in concentrated acid, from which it can be obtained unchanged by dilution with water; (ii) although Rudy and Cramer (*loc. cit.*) reported that it could be diazotized and coupled with 2-aminonaphthalene-3 : 6-disulphonic acid in strongly acid medium, we could not obtain an azo-dye when the substance was diazotized and treated with β-naphthol dissolved in alkali; (iii) it was recovered unchanged in 60% yield after it had been boiled under reflux with acetic anhydride for 6 hours.

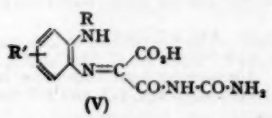
Against formula (I), on the other hand, must be set the observations reported by Kühling and Kaselitz (*loc. cit.*) that the compounds formed from their *N*-monosubstituted *o*-phenylenediamines and alloxan had the following properties: (i) when treated with very dilute alkali, they added a molecule of water, but very easily lost it again when dried in a desiccator; this was assumed to proceed *via* the open-ring compound (V); (ii) one of their compounds gave an acetyl derivative [postulated as (VI)]; (iii) another of their compounds could be converted by the action of hot acid into a substance which contained an additional alloxan fragment and which they thought to have the structure (VII).

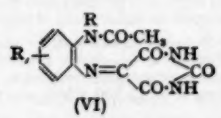
Finally, Rudy and Cramer (*loc. cit.*; *Ber.*, 1939, **72**, 227, 728; *Österreich. Chem. Ztg.*, 1939, **42**, 329) stated that all the compounds from alloxan and *o*-phenylenediamines (whether diprimary or primary-secondary) were similar to that which they obtained from *NN*-dimethyl-*o*-phenylenediamine and alloxan and which they naturally thought must have the anil formula. This statement is open to dispute. While it seems very likely that the compounds from diprimary and from primary-secondary *o*-diamines are similar in structure, Rudy and Cramer themselves pointed out that their compound from *NN*-dimethyl-*o*-phenylenediamine was more soluble

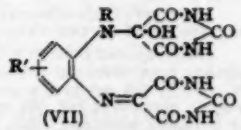


1. *Compound from o-phenylenediamine and alloxan.*
2. *Reduced compound, identical with that obtained from o-phenylenediamine and dialuric acid.*
3. *Compound from* 4 : 5*-dichloro-2-dimethylaminoaniline and alloxan.*
4. *Dihydroketoquinoxalinecarboxylic acid.* 5. *Alloxan.*

in acid, could form a hydrochloride, although this was unstable, and did not give a red colour in concentrated sulphuric as did the other compounds from alloxan and *o*-diamines.

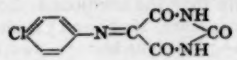

(V)


(VI)

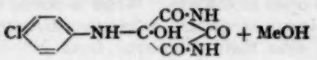

(VII)

For comparison we studied the action of alloxan on 4 : 5-dichloro-2-dimethylaminoaniline in hot acetic acid. As has already been briefly reported (Barlow, *J.*, 1951, 2226) analysis indicates the expected anil plus one molecule of water of constitution. In order to throw light on the structure of this compound, we examined the reaction of alloxan with *p*-chloroaniline. In acetic acid solution, these two formed a bright red compound, $C_{10}H_4O_2N_2Cl$, which was almost certainly the anil (VIII) since it was hydrolysed by dilute acid to *p*-chloroaniline; in methanol they produced a white substance which is very easily dehydrated (in an oven at 120°) to the anil (VIII) and appears to be the carbinol base plus methanol (IX). It seems unlikely that the product from 4 : 5-dichloro-2-dimethylaminoaniline and alloxan can have an anil or hydrated-anil structure because it is stable to the action of hot concentrated hydrochloric

acid. We tried to reach a positive conclusion about the formulæ of these compounds by a study of their catalytic hydrogenation but although both the compound from 4 : 5-dichloro-2-dimethylaminoaniline and the anil (VIII) could be reduced with hydrogen and Raney nickel at room temperature and atmospheric pressure, and the absorption corresponded to the addition



(VIII)



(IX)

of two hydrogen atoms, we obtained a mixture of products in each reduction. The principal reduction product of the compound from 4 : 5-dichloro-2-dimethylaminoaniline was not identical with the compound formed from 4 : 5-dichloro-2-dimethylaminoaniline and dialuric acid; nor with hydrochloric acid did it give a salt identical with that obtained from monochlorobarbituric acid and the diamine. Similarly the principal reduction product of the anil (VIII) did not give with hydrochloric acid a salt identical with that formed from monochlorobarbituric acid and *p*-chloroaniline.

We measured the ultra-violet absorption spectra of the compounds in water, and it is clear that the substance formed from 4 : 5-dichloro-2-dimethylaminoaniline and alloxan does not absorb in at all the same way as the compound from *o*-phenylenediamine and alloxan (figure). If the former is an anil, then the latter is certainly not the anil (II; R = H). Further and more satisfactory evidence is obtained by comparing the absorption of the dihydroketoquinoxaline-carboxylic acid with that of the products from alloxan and *o*-phenylenediamine and from dialuric acid and *o*-phenylenediamine (figure). This leaves little doubt that Hinsberg's original formula is correct. We have not so far confirmed this by synthesis. Examination of the ultra-violet absorption spectra of the compounds obtained by Kühling and others from primary-secondary *o*-diamines should decide whether these too have the same structure (I).

Experimental.

Analyses are by Mr. J. M. L. Cameron and Miss R. H. Kennaway and by Drs. Weiler and Strauss. All m. p.s are uncorrected.

Preparation of the Compound.—When equimolar solutions of *o*-phenylenediamine and alloxan in methanol or water were mixed, a greenish-yellow crystalline porridge was formed within from a minute to a few seconds, depending on the temperature. This was recrystallized from acetic acid; it had m. p. 240° (decomp.) [Hinsberg (*loc. cit.*) recorded m. p. 250° (decomp.)] (Found: C, 51·9; H, 3·5; N, 23·6. Calc. for $C_{10}H_8O_3N_4$: C, 51·7; H, 3·45; N, 24·1%). The yield was almost theoretical. Ultra-violet light absorption in water: maxima at 305 and 385 mμ (ε = 4960 and 964, respectively); minima at 276 and 360 mμ (ε = 2790 and 914, respectively).

Reduction.—The compound (0·5 g.), suspended in methanol, was reduced with hydrogen and Raney nickel at room temperature and atmospheric pressure. The reduction was stopped after the absorption corresponded to the addition of two hydrogen atoms. The mixture was heated to dissolve the reduction product and filtered. The yellow powder (0·4 g.), which separated from the filtrate, was recrystallized from alcohol; the *compound* had m. p. 260° (Found: C, 51·7; H, 3·9; N, 23·9. $C_{10}H_{10}O_3N_4$ requires C, 51·3; H, 4·3; N, 23·9%). Ultra-violet light absorption in water: maxima at 234, 316, and 386 mμ (ε = 19,200, 8850, and 5560); minima at 219, 269, and 354 mμ (ε = 14,800, 2240, and 4180).

The same compound was also produced when equimolar solutions of *o*-phenylenediamine and dialuric acid in methanol were heated under reflux for 2 hours and then left to cool. The yellow needles so formed were recrystallized from ethanol and then had m. p. 260° (Found: C, 51·3; H, 4·4; N, 23·7%) (yield, 80%).

A mixture of this substance and the reduction product also melted at 260° and the ultra-violet absorption spectra of the two materials dissolved in water were identical.

The Compound from 4 : 5-*Dichloro-2-dimethylaminoaniline and Alloxan.*—The preparation of this has already been described (Barlow, *loc. cit.*). A specimen (Found: N, 15·8. Calc. for $C_{12}H_{12}O_4N_4Cl_2$: N, 16·2%) did not give a colour with concentrated sulphuric acid. Ultra-violet light absorption in water: maxima at 249, 286, and 296 mμ (ε = 17,900, 6600, and 6080); minima at 234, 272, and 292 mμ (ε = 12,600, 4590, and 5750).

The Compounds from 4 : 5-*Dichloro-2-dimethylaminoaniline and Dialuric and Chlorobarbituric Acids.*—Equimolar solutions of the diamine and dialuric acid in methanol were boiled under reflux for 2 hours. A yellow substance rapidly separated and was crystallized from a large volume of alcohol. The *compound* did not melt below 320° (Found: C, 41·2; H, 3·5; N, 17·3. $C_{12}H_{12}O_5N_4Cl_2,H_2O$ requires C, 41·2; H, 3·4; N, 16·9%) (yield, 75%). In the same way, equimolar solutions of the diamine and monochlorobarbituric acid in alcohol were boiled under reflux for 1 hour. Orange-yellow crystals were formed when the solution had cooled. These were filtered off and recrystallized from methanol; the *compound* had m. p. 184° (Found: C, 39·4; H, 3·75; N, 15·2. $C_{12}H_{12}O_5N_4Cl_2$ requires C, 39·3; H, 3·5; N, 15·5%).

Model Experiments with p-*Chloroaniline.*—(i) Equimolar solutions of alloxan and *p*-chloroaniline in hot glacial acetic acid were mixed and left overnight. The solvent was distilled off under reduced pressure, and the red residue was extracted with ether in a Soxhlet apparatus. The red anil which

crystallized from the hot ether (m. p. 232°) was recrystallized from acetone by the addition of light petroleum (b. p. 40—60°); it then had m. p. 239° (decomp.) (Found: C, 47·6; H, 2·5; N, 16·7. $C_{19}H_4O_3N_4Cl$ requires C, 47·8; H, 2·4; N, 16·7%) (yield, 60—70%). The *anil* was very soluble in alcohols, acetone, and glacial acetic acid, less in ethyl acetate, slightly in ether and chloroform, very slightly in benzene, and not at all in light petroleum (b. p. 40—60°). When it was treated with 2N-hydrochloric acid in the cold, followed by 2N-sodium hydroxide until alkaline, *p*-chloroaniline (40%; m. p. 67—68°) was recovered. Beilstein and Kurbatow (*Annalen*, 1875, **176**, 29) recorded m. p. 69—70°. No *p*-chloroaniline was isolated when the compound was treated directly with alkali.

(ii) Equimolar solutions of *p*-chloroaniline and alloxan in methanol were mixed and after a time varying from a day, if the solutions were at room temperature, to minutes, if they were hot, a white solid began to separate. The crude, slightly pink product was filtered from the red mother-liquor and left to dry in air. The yield almost theoretical. The *substance* was unstable in solution and formed deep red solutions in solvents such as alcohol or glacial acetic acid. It became red above 120° and finally decomposed, becoming black, at 238—239°. It was insoluble in water but crystallized from 50% aqueous methanol (Found: C, 43·6; H, 3·4; N, 14·1. $C_{11}H_{13}O_5N_3Cl$ requires C, 43·8; H, 4·0; N, 13·9. Loss in weight when dried at 110—120°, 16·5, 16·6. $C_{19}H_4O_3N_3Cl + CH_4O + H_2O$ requires 16·9%). The product of dehydration, m. p. 238—239° (decomp.), was identical with the anil formed in acetic acid. When shaken with cold dilute alkali the substance was rapidly converted into *p*-chloroaniline, m. p. 66—68°.

(iii) Equimolar solutions of monochlorobarbituric acid and *p*-chloroaniline in methanol were mixed; after a few seconds a precipitate formed. This was left overnight, then filtered off and recrystallized twice from 30% aqueous methanol; the *compound* had m. p. 217—218° (decomp.) (Found: C, 41·6; H, 3·2; N, 14·0. $C_{16}H_9O_3N_3Cl_2$ requires C, 41·4; H, 3·1; N, 14·5%). The yield was almost theoretical. The substance was converted into *p*-chloroaniline, m. p. 67—68°, by treatment with alkali.

The Dihydrohetoquinoxalinecarboxylic Acid.—This was prepared from the compound $C_{19}H_8O_3N_4$ by the action of either cold 2N-sodium hydroxide overnight or boiling 4N-sodium hydroxide until no more ammonia was evolved (6 hours). The compound was precipitated with acid and recrystallized from ethanol; it had m. p. 260—261° (decomp.) (Found: C, 57·3; H, 3·4; N, 14·8. Calc. for $C_9H_6O_3N_2$: C, 56·9; H, 3·2; N, 14·7%). Hinsberg (*loc. cit.*) recorded m. p. 265°. Ultra-violet light absorption in water: maxima at 229, 297, and 347 mμ (ε = 14,100, 5030, and 5000); minima at 267 and 321 mμ (ε = 2630 and 4180).

We are indebted for much helpful discussion to Drs. R. A. Raphael and J. C. D. Brand, to the latter especially for interpretation of the ultra-violet absorption spectra. One of us (R. B. B.) is grateful to the Medical Research Council for a training grant during part of the time and for the rest of it to the University of Glasgow for the award of an I.C.I. Fellowship.

Department of Pharmacology, Oxford.
Department of Chemistry, The University, Glasgow. [*Received, June 26th*, 1951.]

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716. *Studies in Co-ordination Chemistry. Part X.* The Vapour Pressure and Heats of Vaporisation of the Stannic Halides.*

By A. Kabesh and R. S. Nyholm.

The development of some ideas concerning the stability of co-ordination compounds is outlined. We have determined the vapour pressures of stannic chloride, bromide, and iodide, using an all-glass membrane manometer (see *J.*, 1951, 3252) as a null instrument for the pressure measurement. Details are given of the methods used for the purification and handling in a vacuum of these compounds. For the three halides the vapour pressure–temperature relation is represented by the general equation $\log P = A - B/T$ over the temperature range investigated, A and B being different constants for each compound. The heats and entropies of vaporisation are calculated. The boiling points at atmospheric pressure are: $SnCl_4$, 113·9°; $SnBr_4$, 205·0°; SnI_4, 348·4°.

In previous Parts of this series, complexes of certain transition metals with tertiary arsines were investigated (*J.*, 1950, 843, 848, 851, 857, 2061, 2071; 1951, 38, 2602). Arising out of this and other work dealing with the metal complexes of tertiary amines, phosphines, and arsines, some tentative generalisations have emerged concerning the nature of the metal–ligand bond in these compounds. It is suggested † that, other factors being equal (*e.g.*, steric effects being absent and the number of lone pairs of electrons on L being the same), the relative

* Part IX, *J.*, 1951, 2602.
† The views now outlined have been described in greater detail by Nyholm (Thesis, London, 1950).

strengths of attachment of a series of ligands of the type LR_3 (L = N, P, As, etc.) or LR_2 (L = O, S, Se, Te) to a metal atom M is determined chiefly by two main factors:

(*a*) The product $\chi_L \times \chi_M$, where χ_L and χ_M are the effective electronegativities of the donor atom L of the ligand, and of the metal M, respectively. For covalent bonds, Gordy (*J. Chem. Physics*, 1946, **14**, 305) and Walsh (*J.*, 1948, 398) have suggested that the bond-force constant may be expressed as a function of the product of the electronegativities of the bonded atoms, and may be taken as a measure of bond strength. An extension of the idea to the co-ordinate link seems reasonable, especially since, once formed, there is really no difference between the two types of bond except that the charges on the atoms will be different. This would presumably alter the effective electronegativities of the two atoms as compared with a covalent bond.

(*b*) The possibility of double-bond formation between L and M involving *d* electrons of the metal M and either a *p* or one of the vacant *d* orbitals of the donor atom L (cf. Pauling, "Nature of the Chemical Bond," 2nd edn., 1940, p. 250; Syrkin, *Bull. Acad. Sci. U.R.S.S.*, Classe Sci. chim., 1948, 69; Syrkin and Dyatkina, "The Structure of Molecules," Butterworth, London, 1950, p. 347; Chatt, *J.*, 1949, 3340; 1951, 652; *Nature*, 1950, **165**, 637).

Thus, in a series of ligands of the Group V elements, of the type LR_3, it was suggested that for co-ordination with boron, aluminium, and other acceptor atoms which have no *d* electrons, the strength of attachment could be explained by the electronegativity effect alone; hence, for these metals the order of strength of attachment should be $NR_3 > PR_3 > AsR_3 > SbR_3$. Although it had been known for some time (Brown and Davidson, *J. Amer. Chem. Soc.*, 1942, **64**, 317) that, towards trimethylaluminium we have the relation $NMe_3 > PMe_3$, yet it was not until recently (Professor Herbert C. Brown, personal communication, 1950) that data for the whole series became available. Professor Brown found that, towards the trimethyl compounds of the Group III metals, the strength of attachment of the Group V ligands is $NR_3 > PR_3 > AsR_3 > SbR_3$, which can be explained as above. However, it would be expected that co-ordination with transition metals, such as nickel, should depend upon both factors since these metals have *d* electrons available and, with the exception of nitrogen, the Group V ligands have vacant higher *d* orbitals which could overlap with a filled *d* orbital of the metal atom to form a π-type bond. The composite bond would then consist of a σ component, decreasing in strength in the sequence N > P > As > Sb, and a π_{d-d} component whose contribution would be nil in the case of nitrogen but important for phosphorus and later elements. The contribution of this π component to the total strength of the bond would depend upon factors such as: (*a*) the relative availability of *d* electron pairs in metals containing a complete sub-shell of 10 *d* electrons (*e.g.*, Sn) and in those in which the *d* shell is incomplete (*e.g.*, Ni), the level of the *d* electrons in both cases being just below that of the bonding orbitals; (*b*) the relative overlaps of the two *d* orbitals, which is dependent upon their relative sizes (see Orgel in report of Co-ordination Chemistry Conference, Wilkins, *Nature*, 1951, **167**, 434). A theoretical investigation of the possible use of *d* orbitals for both σ- and π-bond formation in complex compounds has recently been carried out by Craig, Maccoll, Nyholm, Orgel, and Sutton (to be published shortly).

Further investigation of tertiary amine, phosphine, and arsine complexes is now being carried out in order to obtain quantitative data concerning their order of stability and so enable us to correlate the strength of attachment of the ligand with the nature of the donor atom of the ligand, the metal acceptor, and the ions or groups attached to the metal atom.

Experimentally, the investigation of the strength of attachment of tertiary amines, phosphines, and arsine to Group VIII metals is difficult, and as a start the tin complexes have been chosen for study because the dissociation products are volatile and hence dissociation is accompanied by an increase in pressure which can be measured. Quadrivalent tin readily forms complexes of the type $Sn(Hal)_4,2R_3P(As)$ (Allison and Mann, *J.*, 1950, 2915), and if it is assumed that the σ bonds make use of $5s5p^35d^2$ octahedral bond orbitals of the tin atom, then a filled 4*d* shell is available immediately below these; it was desired to ascertain whether these *d* electrons contribute materially to the strength of the binding of the ligands by forming double bonds.

For this investigation, accurate data were required for the vapour pressures of the tetrahalides, but as these are not to be found in the literature (see also Hildebrand, *J. Chem. Physics*, 1947, **15**, 727), the present investigation was undertaken, the further object being to use these data in the study of the relative stabilities of the tin complexes.

Young (*Sci. Proc. Roy. Dublin Soc.*, 1909—1910, **12**, 374; *J.*, 1891, **59**, 911) determined vapour pressures, specific volumes, and critical constants of the compounds of Group IV

elements with the object of testing the validity of van der Waals's generalisations regarding "corresponding" pressures, temperatures, and volumes. Vapour-pressure measurements on stannic chloride were carried out by a dynamic method with a mercury manometer, the halide being in contact with the mercury of the manometer. Mündel (*Z. physikal. Chem.*, 1913, **85**, 435) studied small vapour pressures at low temperatures both experimentally and theoretically, measuring the vapour pressure of stannic chloride between −53° and −33°. The pressure measurements were made by means of a differential mercury manometer, which, by means of a micrometer screw, measures the difference in level of mercury in a U-tube. Again, however, these measurements were carried out with the halide in contact with mercury. Werthheimer (*Ber. deut. physikal. Ges.*, 1919, **21**, 692), in a theoretical paper, put forward a general form of the vapour-pressure equation. In testing this equation and deductions from it, Werthheimer used experimental data for several compounds, including stannic chloride in the range 30—319°. However, no references, or details of the experimental measurements, were quoted.

Apart from an isolated estimate of the boiling point of stanic bromide at 12 mm. mentioned by Anschütz and Reitter ("Die Destillation unter vermindertem Druck im Laboratorium," 2nd edn., Cohen, Bonn, 1895) we can find no record of vapour-pressure measurements for stannic bromide in the literature. These authors give b. p. 75·8—76·6°/12 mm. and 204·6—204·8°/760 mm., and for the iodide, b. p. 190—190·2°/16 mm. and 295°/760 mm. The only other reliable measurement of heats of fusion and vaporisation of stannic iodide was carried out by Negishi (*J. Amer. Chem. Soc.*, 1936, **58**, 2293) but the vapour-pressure measurements were over a limited range and the extrapolation was so large that the uncertainty in the boiling point could be appreciable.

The practical importance of vapour-pressure data prompted Stull (*Ind. Eng. Chem.*, 1947, **39**, 517, 514) to collect and systematise the available information for a large number of organic and inorganic compounds. All data for a given compound were collected, arranged, and plotted on a Cox chart (Cox, *ibid.*, 1923, **15**, 592; Davis, *ibid.*, 1925, **17**, 735; 1930, **22**, 380; Davis and Calingaert, *ibid.*, 1925, **17**, 1287). A median line was drawn so that it fits the points consistently and temperature values were "read back" at different pressures. The results were then presented in systematic tabular form. The data available for the stannic halides were meagre, in some cases having been measured at two temperatures only. Thus, since the method of analysis is a graphical one, the personal error is an unknown factor and to a fair extent this method of analysis is no better than the data used in its design.

It must be emphasised that in previous work, except that of Negishi (*loc. cit.*), no precautions were taken to avoid contact between the stannic halides and mercury. Young (*loc. cit.*) stated that mercury was attacked by stannic chloride even at low temperatures. According to Dumas (*Ann. Chim. Phys.*, 1862, **33**, 358) stannic chloride reacts with mercury to give both mercurous and stannous chlorides. Moreover, no precautions to exclude moisture were mentioned although the stannic halides hydrolyse readily in moist air, the ease of hydrolysis increasing from the iodide through the bromide to the chloride, which fumes in moist air. The hydrated chloride and bromide usually make ground joints stick together firmly, thus making it impossible to use any stopcocks or ground joints in the main system unless these are rejected afterwards. Stannic iodide decomposes readily in the presence of even small amounts of oxygen or water in the neighbourhood of its boiling point. The great affinity of the halides for water presented the main difficulty in their purification and handling in vacuum, and it was considered desirable to mention in some detail the apparatus and technique used since this largely affects the purity of the compounds and hence the accuracy of the measurements.

Experimental.

Purification and Handling of the Tetrahalides.—Stannic chloride. Chemically pure stannic chloride was further purified by distillation under vacuum in the apparatus shown in Fig. 1A. A flask *c* was provided with a long neck, bent as shown in the diagram; close to the bulb were sealed two side tubes *b* and *d*. A special all-glass seal *e*, separately shown in Fig. 1B, connected the flask *c* to a series of flasks *A*, *B*, *C*, and *D*; the last of these was connected to another seal *h*, the open end of which was sealed to the adapter *l* with a multi-head rotating receiver *m*. The special seals are small, thin-walled capillary tubes sealed in wider tubes in such a manner that the bent capillary tube can be broken at will by means of a small magnetic hammer enclosed in glass. Stannic chloride was introduced through the inlet *a*, which was then sealed off. The flask *c* was cooled in liquid air and thoroughly evacuated through *b*, which was then sealed off. The bulb was heated in an oven at 100° for 12 hours, whereby a white, crystalline sublimate, probably the hydrate, was formed at the cold bent neck which was kept projecting outside the oven. The flasks *A*, *B*, *C*, and *D* were evacuated through *j*, the bulbs and connecting tubes being kept, during the evacuation, as hot as possible to expel any adsorbed water

vapour, and finally *j* was sealed off. The flask *c* was now connected to the rest of the apparatus simply by breaking the capillary tube of the special seal *e*, the magnetic hammer being used. The more volatile part of the liquid was then distilled into *A* by cooling *A* in liquid air. The flask was then sealed off at the constriction *f*, and the contents of *A* rejected. The greater part of the stannic chloride was distilled into *B* in the same way. Two more distillations were carried out, the material being collected in *D*. Each time a residue was left in the flasks, which were sealed off at the constrictions *g*, *h*, and *i* as soon as each distillation was completed. The multihead receiver *m* attached to the adapter *l* was then evacuated and out-gassed through *n*, which was then sealed off. The capillary of the seal *k* was broken and samples of the purified stannic chloride were collected in the receiving tubes. These were previously slightly drawn down and scratched by a file to facilitate breaking them.

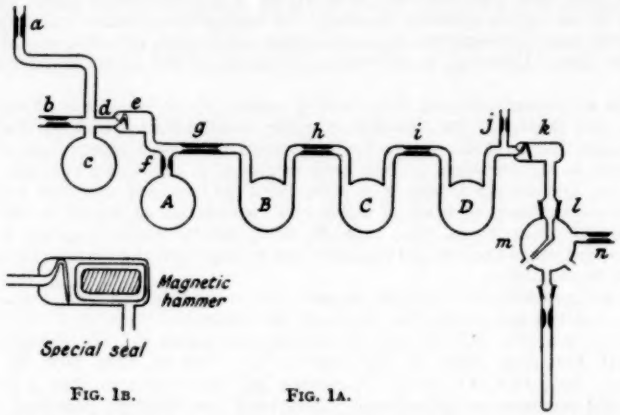
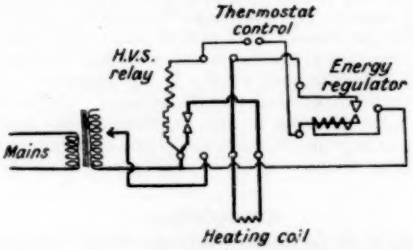


FIG. 1B. FIG. 1A.

Stannic bromide. A B.D.H. product was further purified by fractional distillation under partial vacuum, a Vigreux type column about 30 cm. long being used. Since the m. p. of stannic bromide is slightly above room temperature, it was necessary to warm the receiver with a small flame to prevent the solid from blocking the tubes. The receiving part was exactly the same as that used for stannic chloride, and the same precautions were taken.

Stannic iodide. A B.D.H. product was recrystallised three times from carbon tetrachloride. The crystals were dried in a current of dry air at 120° and finally under vacuum. They were then sublimed and sealed under vacuum in sample tubes (see Fitzgerald, *J. Amer. Chem. Soc.*, 1907, **29**, 1693).

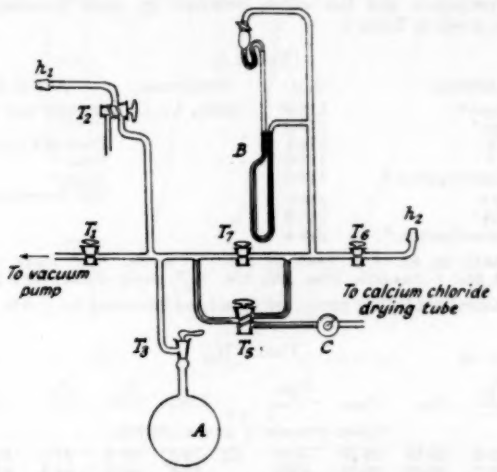
FIG. 2.



The thermostat was made of an aluminium-bronze alloy, which was chosen for its high thermal conductivity and heat capacity. It has a high m. p. and when electrically heated shows no sign of oxidation. The block, a 12″ × 15″ cylinder, had a 2″ × 10″ hole in the centre to take the reaction flask. The block was heated by two nichrome coils; one, an 85-ohms coil, was included in the control circuit, and the second, a 50-ohm coil, was connected directly to the mains through a variable resistance. The latter coil helped in reaching the required temperature rapidly and was immediately switched off when the temperature was within 5° of the required value. For the accurate control of temperature a thermostat regulator was used in combination with a Sunvic energy regulator type TYB and a Sunvic hot-wire vacuum switch type F 102—3M used as a relay. This standard control circuit is illustrated in Fig. 2. Temperature measurements were carried out by means of chromel–alumel thermocouples calibrated against one whose elements had been calibrated by the National Physical Laboratory.

Temperature measurements, recorded by a Cambridge thermocouple potentiometer, were within $\pm 0{\cdot}1°$. Vapour-pressure measurements were carried out by means of an all-glass membrane manometer (see p. 3252). The main vacuum line shown in Fig. 3 consists of a mercury manometer *B*, the closed end of which was provided with a U-type loop and cut-off stopcock (Gilmont, *Ind. Eng. Chem., Anal.*, 1948, **20**, 474). A two-way capillary tap T_3 was connected to the line by a length of capillary tubing, and its free end was connected to a needle valve *C* which ended with a calcium chloride drying-tube, thus allowing dry air to balance the pressure to be measured. A 5-litre flask *A* was connected through the tap T_3; this was used as a vacuum reservoir, in case it was needed whilst carrying out a run, for the pump was always stopped to prevent any vibrations, which affected the glass-membrane

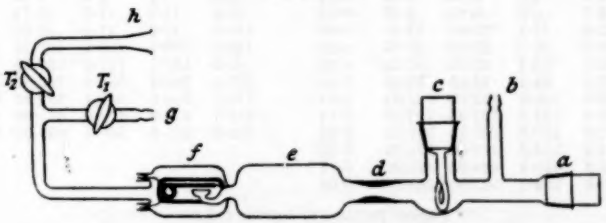
FIG. 3.



manometer. Taps T_1, T_2, T_4, and T_6 were inserted to facilitate manipulation and to separate any part of the vacuum line when necessary.

When carrying out a run, a tube containing the sample was thoroughly cleaned, dried, and introduced through the ground joint at *a* in the apparatus shown in Fig. 4, where it was held in position by the strong loop-hole of the vacuum breaker *c*. The whole part shown in Fig. 4 was connected to the main line by means of the ground joint *h* through the socket h_1 (see Fig. 3) and inclined at an angle of about 20° to the horizontal with the right-hand side uppermost. This inclination was usually sufficient to allow the sample tube to glide easily to the reaction flask *e*. The tubes *b* and *g* were connected together with pressure tubing, and the apparatus was evacuated on both sides of the diaphragm at the same

FIG. 4.



time, a two-stage Speedivac pump being used. The reaction flask was out-gassed, then cooled by ether–solid carbon dioxide. The sample tube was then broken under vacuum simply by turning the tap *c*; meanwhile evacuation was continued. Slight tapping was sometimes necessary to cause the sample tube to fall into the reaction flask. The flask was then cautiously sealed off at the previously made constriction *d*. This step requires care because any fault may lead to the breaking of the glass-membrane manometer. Taps T_1 and T_2 were closed, and the apparatus released from the main line and inserted vertically in the constant-temperature zone of the high-temperature thermostat, while the joint *h* was again connected to the main line at h_2 (see Fig. 3). Evacuation was continued, tap T_3 was opened to the main line and finally the pump was stopped. The block was heated to the required

temperature and kept thereat for at least ½ hour. At every temperature two pressure measurements were recorded; one, p_1, was taken when approaching the temperature from below by heating the block to that temperature; the other reading p_2 was approached from the higher temperature by heating to some temperature above that required and allowing the block to cool to the required value. The zero reading of the manometer was checked over the whole range both before and after a run to ensure that it had remained constant.

Results and Discussion.

The samples used in this investigation are undoubtedly very pure in view of the technique used for their purification. A comparison between the boiling points found for the tetrahalides in this investigation and the values obtained by other investigators, corrected to one atmosphere, are given in Table I.

Table I.

Compound.	Author(s).	B. p.	Compound.	Author(s).	B.p.
$SnCl_4$	Andrews [a]	112·9°	$SnBr_4$	Carnelly and O'Shea [e]	201·0° (uncorr.)
	Thorpe [b]	113·9			
	Young [c]	114·1		Preis and Rayman [f]	203·3
	Bond [d]	112·6		Bond [d]	206·5
	This investigation *	113·9		Rader [g]	206·7
SnI_4	Rader [g]	346·0		This investigation *	205·0
	Negishi [h]	348·0			
	This investigation *	348·4			

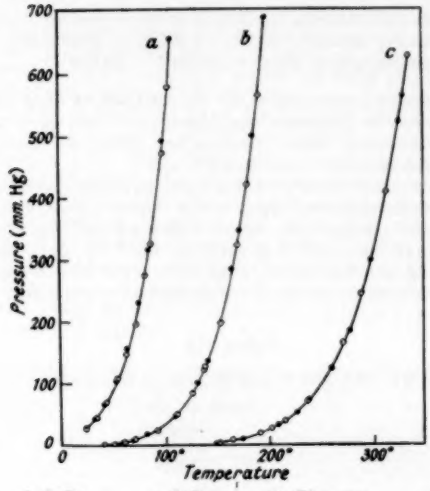
[a] *Chem. News*, 1847, **25**, 61. [b] *J.*, 1880, **37**, 331. [c] *Loc. cit.* [d] *J. Amer. Chem. Soc.*, 1926, **48**, 348. [e] *J.*, 1878, **33**, 55. [f] *Annallen*, 1884, **223**, 324. [g] *Z. anorg. Chem.*, 1923, **130**, 325. [h] *Loc. cit.*

* Estimated boiling points are considered as correct to ± 0·2°.

Table II.

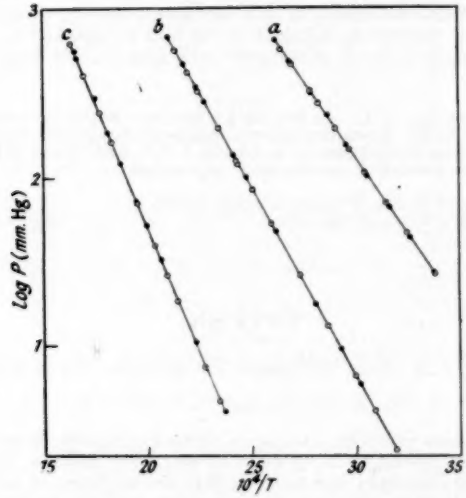
	Temp.	p_1, mm.	p_2, mm.	$P_{obs.}$	$P_{calc.}$	$P_{calc.} - P_{obs.}$		Temp.	p_1, mm.	p_2, mm.	$P_{obs.}$	$P_{calc.}$	$P_{calc.} - P_{obs.}$
					Vapour pressure of stannic chloride.								
(1)	22·5°	26·5	26·5	26·50	26·50	0·00	(2)	23·2°	27·4	27·2	27·30	27·41	0·11
	34·8	46·9	46·7	46·80	46·80	0·00		33·5	44·1	44·1	44·10	44·12	0·02
	44·4	70·6	70·7	70·65	70·63	−0·02		42·8	66·1	66·0	66·05	66·07	0·02
	54·7	107·1	107·2	107·15	107·13	−0·02		53·4	101·9	101·7	101·80	101·76	−0·04
	62·9	146·3	146·4	146·35	146·39	0·04		64·5	155·4	155·5	155·45	155·02	−0·43
	70·9	195·8	195·6	195·70	195·70	0·09		75·5	230·3	230·4	230·35	230·14	−0·21
	80·9	274·4	274·4	274·40	274·74	0·07		84·7	314·1	314·0	314·05	313·69	−0·36
	85·7	324·1	324·1	324·10	324·12	0·02		98·8	490·0	490·0	490·00	489·32	−0·68
	97·6	471·7	471·6	471·65	471·65	0·09		108·5	653·3	653·2	652·25	652·23	−1·02
	104·3	577·3	577·3	577·30	577·34	0·04							
					Vapour pressure of stannic bromide.								
(1)	40·0°	2·4	2·4	2·40	2·39	−0·01	(2)	57·8	5·8	5·9	5·85	5·86	0·01
	50·3	4·1	4·0	4·05	4·06	−0·01		68·0	9·4	9·4	9·40	9·40	0·00
	60·4	6·7	6·6	6·65	6·63	−0·02		82·8	17·7	17·8	17·75	17·78	0·03
	74·9	13·0	13·1	13·05	13·07	0·02		108·6	47·9	47·9	47·90	48·01	0·11
	92·5	26·2	26·2	26·20	26·26	0·06		130·3	100·1	100·2	100·15	100·30	0·15
	111·5	53·1	53·2	53·15	53·24	0·09		140·3	137·1	137·2	137·15	137·25	0·10
	125·3	85·2	85·1	85·15	85·25	0·10		165·5	283·9	283·8	283·85	283·85	0·00
	136·5	122·0	122·0	122·00	122·04	0·04		173·2	348·5	348·4	348·45	348·66	0·21
	137·9	127·4	127·3	127·35	127·47	0·12		185·7	479·6	479·6	479·60	479·84	0·24
	152·6	197·7	197·8	197·75	197·79	0·04		199·8	689·6	689·6	689·60	689·75	0·15
	170·5	324·5	324·5	324·50	324·72	0·22							
	180·5	420·8	420·9	420·85	421·02	0·17							
	192·3	563·8	564·0	563·90	563·90	0·00							
					Vapour pressure of stannic iodide.								
(1)	152·4	4·7	4·8	4·75	4·75	0·00	(2)	148·6	4·1	4·1	4·10	4·11	0·01
	165·5	7·7	7·7	7·70	7·69	−0·01		174·2	10·5	10·4	10·45	10·43	−0·02
	192·0	18·7	18·7	18·70	18·71	0·01		209·9	32·3	32·4	32·35	32·27	−0·08
	203·1	26·3	26·4	26·35	26·37	0·02		226·9	52·3	52·3	52·30	52·26	−0·04
	2616·6	39·2	39·2	39·20	39·19	−0·01		239·6	73·3	73·3	73·30	73·35	0·05
	237·1	70·6	70·5	70·55	70·53	−0·02		260·1	122·6	122·6	122·60	122·57	−0·03
	272·5	164·1	164·2	164·15	164·10	−0·05		278·4	187·5	187·5	187·50	187·67	0·17
	290·2	243·4	243·3	243·35	243·61	0·26		299·9	299·2	299·3	299·25	299·16	−0·09
	315·1	407·5	407·5	407·50	407·38	−0·12		327·6	518·7	518·8	518·75	518·80	0·05
	337·6	625·6	625·6	625·60	625·46	−0·14		332·0	563·8	563·7	563·75	564·00	0·25

FIG. 5.



a, $SnCl_4$. *b*, $SnBr_4$. *c*, SnI_4. ○ *First run.* ● *Second run.*

FIG. 6.



a, $SnCl_4$. *b*, $SnBr_4$. *c*, SnI_4. ○ *First run.* ● *Second run.*

The vapour-pressure data for the three halides are given in Table II. Results are given for two runs on each compound. Pressures are considered to be accurate to better than $\pm 0{\cdot}2$ mm. In the tables p_1 and p_2 have the meaning given above, and $P_{obs.}$ represents the mean value of p_1 and p_2. The variation of $P_{obs.}$ with temperature is shown in Fig. 5. In Fig. 6, values

of log $P_{obs.}$ are plotted against $1/T$. The vapour pressure–temperature relationships for the three compounds are represented by the following equations:

$$\text{stannic chloride, } \log P = 7{\cdot}59676 - 1824{\cdot}9/T$$
$$\text{stannic bromide, } \log P = 7{\cdot}63048 - 2270{\cdot}8/T$$
$$\text{stannic iodide, } \log P = 7{\cdot}66607 - 2973{\cdot}9/T$$

These equations were derived empirically by the method of least squares. The two last columns in Table II give the pressures calculated from the equations and the differences between observed and calculated value. Only in one case is the deviation more than 1 mm. and in most cases the agreement is better than 0·3 mm.

By assuming that the molal volume of the liquid is negligible compared with that of the vapour, and that the perfect-gas laws apply to the vapour phase, one can put the Clausius–Clapeyron equation in the simple form, $\Delta H = -\boldsymbol{R}\mathrm{d}(\ln p)/\mathrm{d}(1/T)$, where ΔH is the heat of vaporisation in calories per mole and $\boldsymbol{R}$ is taken as 1·987 cal. deg.$^{-1}$ mole^{-1}. By use of this equation the heats of vaporisation of the tetrahalides have been calculated; these are given in Table III, which also shows the value of the entropy of vaporisation in each case.

TABLE III.

Heats and entropies of vaporisation of the stannic halides.

	ΔH, cal./mole.	ΔS, cal./mole/degree.
$SnCl_4$	8,350	21·6
$SnBr_4$	10,390	21·7
SnI_4	13,610	21·9

Our value for the latent heat of vaporisation of stannic chloride, namely, 32·1 cal./g., is in reasonably good agreement with the value of 32·6 cal./g. obtained by calculation by Hammick (*Phil. Mag.*, 1922, **44**, 590), who used the expression $\lambda_{vap.} = \lambda_{ex.} + H + h$, where $\lambda_{vap.}$ is the heat of vaporisation at the normal boiling point, $\lambda_{ex.}$ is the heat of expansion, H is the heat due to the change of internal energy of the substance occurring during the transformation from the liquid to the vapour phase, and h is the heat of association. For stannic iodide, our value of 13,610 cal./mole agrees satisfactorily with that given by Negishi (*loc. cit.*), namely, 13,650 cal./mole.

The authors are indebted to Dr. A. Maccoll for his very helpful criticism. The award of an I.C.I. Fellowship (to R. S. N.), during the tenure of which this investigation was started, is gratefully acknowledged. The advice of Professor C. K. Ingold, F.R.S., and Professor E. D. Hughes, F.R.S., and their criticism of the manuscript are also much appreciated.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES
UNIVERSTIY COLLEGE, LONDON.

[*Received, April 17th*, 1951.]

NOTES.

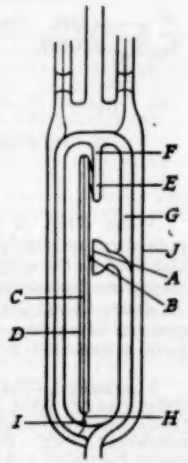
717. *A New All-glass Membrane Manometer.*

By A. KABESH and R. S. NYHOLM.

IN pressure measurements involving substances which are capable of attacking mercury all-glass manometers have proved to be of great value. They may be used as direct-reading instruments after being calibrated, but as a rule they are employed as null instruments. The gauge which changes its shape when pressure is applied inside or outside indicates a balance between the pressure to be measured, *e.g.* of the corrosive gas, and an adjustable known pressure usually measured by a mercury manometer. In both methods for using the gauge the deformation is suitably magnified and followed by a convenient apparatus. Several manometers of this type are described in the literature, a summary of which is given by Partington ("An Advanced Treatise on Physical Chemistry," Longmans, Green and Co., 1950, Vol. I, p. 656). Our experience in the use of manometers over a fairly wide range of

temperature, involving successive heating and cooling of the gauge, has shown that many of these devices are unsatisfactory. The chief difficulty lies in the magnification system which is frequently affected by variation in temperature. Furthermore, whilst most gauges are sensitive and reliable when used at a fixed temperature or over a small range in temperature, the zero setting of the gauge is usually found to be subject to large and inconsistent changes with change in temperature. By zero setting is meant the small positive pressure applied on the diaphragm to make or break an electrical circuit.

Some experimenters have tried to overcome this difficulty by keeping the dead space at the head of the gauge as small as possible and at the same time keeping the head separately heated to a constant temperature. Others have tried to calibrate the gauge before using it. The first method has the disadvantage that there is a temperature gradient between one end of the reaction vessel and the other. We have found the second method unsuitable because successive heating and cooling of the gauge gave inconsistent zero readings. These difficulties called for the construction of a gauge which should conform to the following requirements: (*a*) the gauge must be sensitive to at least 0·1 mm. Hg, and at the same time be rigid enough to withstand fairly large pressure differences without breaking; (*b*) the adjustment of the contact points should be fairly simple; (*c*) the zero setting of the gauge should be reproducible.



The Apparatus.—The gauge shown in the figure substantially fulfils the requirements detailed above. The actual dimensions of an instrument of this type depend upon the circumstances for which it is required; in our own case the dimensions are given below. The membrane *A* (1·5—2·0 cm. in diameter) was made as thin as possible, consistent with the necessary mechanical strength; the thickness was not measured. Several membranes were blown and a suitable one chosen from these. The head of the gauge was bent so that the membrane *A* was in a vertical position, and a glass rod *G* was sealed to it to act as a supporting frame. The lever *D*, 10 cm. long, was made by sealing a platinum wire *C*, 0·45 mm. in diameter, in a glass capillary tube 3 mm. in external diameter. One end of the lever was sealed to a glass spiral *E* consisting of 2 turns, of approximately 2·5 cm. diameter, of glass rod, 0·3 cm. in diameter; the spiral was then sealed to the frame at *F*. Meanwhile, the glass pip *B* was made to rest with slight pressure on the membrane at the point of maximum tilting. According to Frank and Bromeser's theory for the bending of a plate of this type (*Sitzungsber. Ges. Morphol. Physiol.*, 1912, **28**, 45) the point of maximum tilting occurs at a point $r/\sqrt{3}$ from the centre. The platinum tip *H*, which was left uncovered at the end of the lever, should be only just making contact with the platinum stirrup *I*, sealed to the frame. The adjustment of the contact points was then completed before sealing the assembly in the outer jacket *J*. Once this adjustment has been made the apparatus should need no further attention. It is advisable to have the lever in a vertical position parallel to the plane of the membrane, thus reducing the effect of gravity.

In this gauge an attempt has been made to eliminate the usual factors which normally result in an irregular variation of the zero setting, but it is obvious that nothing can be done to change the inherent properties of the glass itself. The variation of the zero setting with temperature is linear and is affected by both the diameter and the thickness of the diaphragm. Other things being equal, the zero setting was found to increase with increasing temperature, possibly owing to the variation of the modulus of elasticity of glass with temperature. It is of interest to note that a gauge of this type, but made of silica, showed a decrease in zero setting with increasing temperature. Silica, unlike most elastic solids, shows an increase in its modulus of elasticity with increase of temperature.

This gauge has been used successfully in the measurement of the vapour pressures of the stannic halides over the temperature range from room temperatures to about 340° (see *J.*, 1951, 3245).

The authors are indebted to Mr. Sharaf El-Din and Mr. J. Frost for technical assistance in the development of this manometer.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON.

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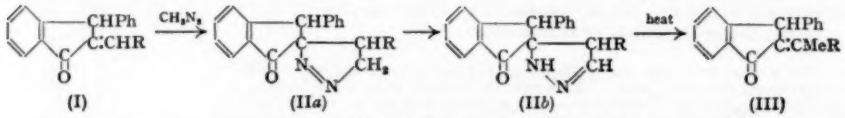
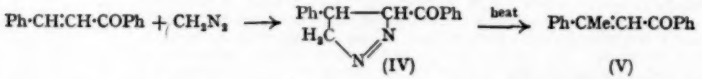
718. *Action of Diazomethane on 2-Arylidene-3-phenylindan-1-ones.*

By Ahmed Mustafa and Mustafa Kamal Hilmy.

In continuation of investigations on the action of diazomethane on aromatic compounds (Schönberg and Mustafa, *J.*, 1946, 746; 1948, 605; Schönberg, Mustafa, and Hilmy, *J.*, 1947, 1045; Mustafa, *J.*, 1949, 234), the behaviour of the 2-arylidene-3-phenylindan-1-ones listed in Table I towards diazomethane in ether–methanol has been studied. In all cases the coloured starting materials (I) were transformed into colourless or almost colourless substances (II*a* or *b*) containing active hydrogen. Structure (II*b*) is preferred, and (II*a*) is regarded as an intermediate product. These products were decomposed by heat to the alkylated ethylenes (III) [cf. the thermal decomposition of 3-benzoyl-4-phenyl-Δ^1-pyrazoline (IV) obtained by the action of ethereal diazomethane on benzylideneacetophenone], which yielded the dypnone (V) (Smith and Pings, *J. Org. Chem.*, 1937, **2**, 23; Smith and Howard, *J. Amer. Chem. Soc.*, 1943, **65**, 159).





When (III; R = C_6H_4·OMe-*p*) is treated with alcoholic hydrochloric acid or (15%) potassium hydroxide, it yielded *p*-methoxyacetophenone and 3-phenylidan-1-one, which were identified as the corresponding 2 : 4-dinitrophenylhydrazones (cf. the hydrolysis of 2-hydroxymethylene-3-phenylindan-1-one with 2% potassium hydroxide; Johnson and Shelberg, *J. Amer. Chem. Soc.*, 1945, **67**, 1758). The action of hydroxylamine hydrochloride in the presence of aqueous sodium hydroxide on (III; R = C_6H_4·OMe-*p*) or (I; R = C_6H_4·OMe-*p*) gave, as expected, 3-phenylidan-1-one oxime.

Experimental.—Substituted 2-Arylidene-3-phenylindan-1-ones (I).—3-Phenylindan-1-one (0·1 mol.) (Pfeiffer and de Waal, *Annalen*, 1935, **520**, 185) and the appropriate aldehyde (0·1 mol.) in ethyl alcohol (15 c.c.) were treated with 10% aqueous sodium hydroxide (1·5 c.c.), whereupon the 2-arylidene derivative separated quickly. It was filtered off, washed with water, and recrystallised from benzene. The yellow 2-*arylidene* compounds listed in Table I were thus prepared; all gave yellow or orange solutions in cold concentrated sulphuric acid.

Table I.

Substituted 2-arylidene-3-phenylindan-1-ones (I).

Aryl =	M. p.	Yield, %	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
Phenyl [a]	158°	85%	$C_{22}H_{16}O$	89·2	5·4	89·2	5·4
o-C_6H_4·OMe	199	70%	$C_{23}H_{18}O_2$	84·6	5·5	84·7	5·5
p-C_6H_4·OMe [a]	174	82%	$C_{23}H_{18}O_2$	84·5	5·3	84·7	5·5
p-C_6H_4Me	220	80%	$C_{23}H_{18}O$	89·2	5·7	89·0	5·8
m-C_6H_4·NO_2	194	36%	$C_{22}H_{15}O_3N$ [b]	77·2	4·0	77·4	4·4
o-C_6H_4Cl	140	62%	$C_{22}H_{15}OCl$ [c]	80·0	4·5	79·9	4·5
2-Furyl	160	45%	$C_{20}H_{14}O_2$	84·0	4·7	83·9	4·9

[a] Pfeiffer and de Waal, *loc. cit.*
[b] Found: N, 4·0. Reqd.: N, 4·1%.
[c] Found: Cl, 10·5. Reqd.: 10·7%.

Action of Diazomethane on 2-Arylidene-3-phenylindan-1-ones. 2-*p*-Methoxybenzylidene-3-phenylindan-1-one (I; R = C_6H_4·OMe-*p*) (1 g.) (Pfeiffer and de Waal, *loc. cit.*) in cold methyl alcohol (1 c.c.) was treated with an excess of cold, ethereal diazomethane solution [from nitrosomethylurea (8 g.)], and the mixture left at 0° for 72 hours, during which fresh amounts of etheral diazomethane solution were added. The ether was then evaporated off and the resulting colourless crystals were collected, washed with light petroleum (b. p. 40—60°), and crystallised from benzene–light petroleum (b. p. 40—60°) with decomposition. 3-*Phenylindan-1-one-2-spiro-2′-(4′-p-methoxyphenyl-*Δ^1*-pyrazoline*) (II; R = C_6H_4·OMe-*p*), m. p. 124°, is easily soluble in benzene or hot ethyl alcohol, but difficultly soluble in light petroleum (b. p. 50—60°) (Found: C, 78·1; H, 5·2; N, 7·5. $C_{24}H_{20}O_2N_2$ requires C, 78·2; H, 5·4;

N, 7·6%). The *pyrazoline* derivatives listed in Table II were similarly prepared; they were crystallised from benzene–light petroleum, and in cold concentrated sulphuric acid gave yellow or orange solutions with much decomposition.

TABLE II.

Substituted pyrazoline derivatives (II).

R	M. p.[a] (decomp.)	Formula	Found, % C	Found, % H	Found, % N	Required, % C	Required, % H	Required, % N
Ph	120—122°	$C_{23}H_{18}ON_2$	81·5	5·3	7·9	81·6	5·3	8·3
o-C_6H_4·OMe	118	$C_{24}H_{20}O_2N_2$ [a]	78·1	5·6	7·2	78·2	5·4	7·6
p-C_6H_4·OMe	124	$C_{24}H_{20}O_2N_2$	78·0	5·2	7·5	78·2	5·4	7·6
p-C_6H_4Me	133—134	$C_{24}H_{20}ON_2$	81·7	5·7	7·9	81·8	5·7	7·95
m-C_6H_4·NO_2	136	$C_{23}H_{17}O_3N_3$	71·8	4·3	10·8	72·1	4·4	10·97
o-C_6H_4Cl	125	$C_{23}H_{17}ON_2Cl$ [b]	74·0	4·6	7·3	74·1	4·6	7·5
Furyl	128	$C_{21}H_{16}O_2N_2$	76·5	4·5	8·2	76·8	4·8	8·5

[a] Found: Active H, 0·26. Reqd.: Active H, 0·27%. [b] Found: Cl, 9·3. Reqd.: Cl, 9·5%. The compounds were recrystallised from benzene–light petroleum (b. p. 40—60°). In cold, concentrated sulphuric acid, they give yellow to orange solutions with strong decomposition.

Thermal Decomposition of the Pyrazoline Derivatives (II).—(*a*) The spiran (II; R = C_6H_4·OMe-*p*) was heated at 200° (bath-temp.) in a stream of dry carbon dioxide for 0·5 hour. The product, after cooling, was extracted several times with ligroin (b. p. 60—80°); the extracts were evaporated slowly and the resulting yellow crystals of 2-(p-*methoxy-α-methylbenzylidene*)-3-*phenylindan*-1-*one* (m. p. 145°) were filtered off and recrystallised from ethyl alcohol (Found: C, 84·4; H, 5·6. $C_{24}H_{20}O_2$ requires C, 84·7; H, 5·9%). The compound is easily soluble in benzene, but difficulty soluble in light petroleum (b. p. 30—50°) and gives an orange solution with concentrated sulphuric acid.

(*b*) The *o*-methylphenyl isomer (II) was heated at 180° (bath-temp.) for 15 minutes. The *o-methoxybenzylidene* compound (III) formed pale yellow crystals (from ethyl alcohol), m. p. 158—159° (Found: C, 84·5; H, 5·8. $C_{24}H_{20}O_2$ requires C, 84·7; H, 5·9%). It is easily soluble in benzene or acetic acid but difficultly soluble in light petroleum (b. p. 40—60°), and gives a yellowish-orange colour with sulphuric acid.

(*c*) The p-*methylbenzylidene* derivative (III), obtained at 220° (0·5 hour), forms in yellow crystals, m. p. 145—146°, from ethyl alcohol (Found: C, 88·6; H, 6·3. $C_{24}H_{20}O$ requires C, 88·9; H, 6·2%). It gives a yellow solution with sulphuric acid and is easily soluble in benzene or chloroform.

Behaviour of the Olefin (III; R = C_6H_4·OMe-*p*) *towards* (a) *alcoholic hydrochloric acid, and* (b) *alcoholic potassium hydroxide*.—(*a*) The olefin (III; R = C_6H_4·OMe-*p*) was heated under reflux with alcoholic hydrochloric acid [ethyl alcohol (10 c.c.); hydrochloric acid (*d* 1·18) (5 c.c.)] for 3 hours, during which fresh amounts of the acid (about 5 c.c.) were added. On cooling, the reaction mixture was poured into water, extracted with ether, washed with dilute aqueous sodium carbonate and then water, and dried (Na_2SO_4), and the ether evaporated off. The oily residue was washed several times with cold light petroleum (b. p. <40°); some material (*A*) was insoluble. The light petroleum solution was evaporated; the solution of the oily residue in acetic acid was treated with 2 : 4-dinitrophenylhydrazine in acetic acid, and the reaction mixture refluxed for 10 minutes. On concentration and cooling, orange-red crystals of *p*-methoxyacetophenone 2 : 4-dinitrophenyl hydrazone separated, which after recrystallisation from acetic acid had m. p. and mixed m. p. 220°. The insoluble material (*A*) gave similarly 3-phenylindane-1-one hydrazone, orange-red crystals (from acetic acid), m. p. 218° (m. p. and mixed m. p. with an authentic specimen) (Found: C, 64·6; H, 4·1; N, 14·3. $C_{21}H_{16}O_4N_4$ requires C, 64·9; H, 4·1; N, 14·4%).

(*b*) A solution of the olefin (0·5 g.) in ethyl alcohol (10 c.c.) and 15% alcoholic potassium hydroxide (5 c.c.) were refluxed for 3 hours. The reaction mixture was poured into water and worked up as above, giving the same products.

Similarly, the *p*-methylbenzylidine compound (III; R = C_6H_4·Me-*p*) and alcoholic potassium hydroxide led to *p*-methylacetophenone and 3-phenylindan-1-one, which were identified as the corresponding 2 : 4-dinitrophenylhydrazones (m. p. and mixed m. p.).

Action of Hydroxylamine Hydrochlorides on 2-p-Methoxybenzylidene-3-phenylindane-1-*one*.—The compound (I; R = C_6H_4·OMe-*p*) (0·3 g.) and hydroxylamine hydrochloride (0·4 g.) in ethyl alcohol (10 c.c.) and alcoholic potassium hydroxide [potassium hydroxide (0·7 g.); water (0·5 c.c.); ethyl alcohol (5 c.c.)] were refluxed for 3 hours (water-bath). The reaction mixture was poured into acidified ice-cold water, extracted with ether, washed with water, dried (Na_2SO_4), and evaporated. The colourless crystals of 3-phenylindan-1-one oxime that separated were recrystallised from ethyl alcohol, and had m. p. and mixed m. p. 143° (Found: C, 80·5; H, 5·7; N, 6·4. Calc. for $C_{15}H_{13}ON$: C, 80·7; H, 5·8; N, 6·3%) (Liebermann and Hartmann, *Ber.*, 1892, **25**, 2124, gave m. p. 141°).

The analogues (I; R = C_6H_4·OMe-*o* and C_6H_4Me-*p*), and the compounds (III; R = C_6H_4·OMe-*o* and -*p*, and C_6H_4Me-*p*) behaved similarly.

CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE,
FOUAD I UNIVERSITY, ABBASSIA, CAIRO.

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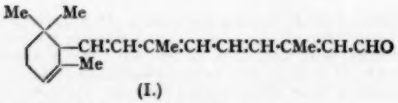
719. *Isomers of Retinene 2 : 4-Dinitrophenylhydrazone.*

By Marc Julia and B. C. L. Weedon.

Recently Braude and Forbes (*J.*, 1951, 1762) reported the oxidation of vitamin A by 2 : 4-dinitrophenylhydrazine in acid solution to an aldehyde which was isolated as its 2 : 4-dinitrophenylhydrazone. This derivative, m. p. 204°, was isomeric with that, m. p. 208°, prepared directly from retinene (vitamin-A aldehyde), and exhibited maximum light absorption at a wave-length (4220 Å) considerably shorter than that (4420 Å) of the authentic derivative. Braude and Forbes suggested that the lower-melting derivative may be either a geometrical isomer of retinene 2 : 4-dinitrophenylhydrazone, or a derivative of an isomer (I) of retinene, formed during the oxidation reaction by migration of the cyclic double bond out of conjugation with the polyene side chain. In view of this publication it seems of interest to record that a derivative, which is believed to be identical with that of Braude and Forbes, was synthesised in the following manner.

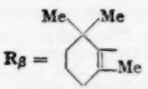


(I.)

(III.) Rβ·CH_2·CH:CMe·CHO HC:C·CMe(OH)·CH:CH_2 (II.)

Rβ·CH_2·CH:CMe·CH(OH)·C:C·CMe(OH)·CH:CH_2 (IV.)

Rβ·CH_2·CH:CMe·CH(OH)·CH:CH·CMe(OH)·CH:CH_2 (V.)



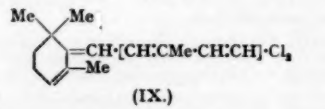
Reaction of the Grignard complex from 1-chloro-3-methylpent-1-en-4-yn-3-ol (II) with the C_{14} aldehyde (III) yielded the crystalline glycol (IV). Partial hydrogenation of the latter and treatment of the resulting crude ethylenic glycol (V) with methanolic 2 : 4-dinitrophenylhydrazine sulphate (Brady's reagent) led to a 2 : 4-dinitrophenylhydrazone, m. p. 203° ($\lambda_{max.}$ 4190 Å). No depression in melting point was observed on admixture of this derivative with that prepared by Braude and Forbes, but the melting points of both were depressed on admixture with an authentic specimen of retinene 2 : 4-dinitrophenylhydrazone.

The formation of derivatives of αβ-unsaturated aldehydes (VI) has also been observed on addition of Brady's reagent to chlorovinylcarbinols (VII), where R is alkyl, aryl, acetylenyl, or vinyl (cf. Julia, *Ann. Chim.*, 1950, **5**, 595). With the exception of (VII; R = CH_2:CH),

(VII.) (VI.)

CH_2(OH)·CH:CMe·CH:CH_2

(VIII.)



(IX.)

Rβ·CH_2·CH(OMe)·CMe:CH·C:C·CMe:CH·CHO (X.)

these alcohols yield the aldehydes (VI) themselves on treatment with mineral acids (*idem, loc. cit.*; Jones and Weedon, *J.*, 1946, 937). The carbinol (VII; R = CH_2:CH) under similar conditions gives the isomer (VIII) and not the aldehyde (VI; R = CH_2:CH), the derivative of which is obtained by the action of Brady's reagent (Julia, *loc. cit.*).

Attempts to convert the glycol (V) into retinene, or its isomer (I), were unsuccessful. Treatment of (V) with a solution of iodine in toluene gave a halogen compound which did not react with carbonyl reagents but exhibited light-absorption properties similar to those of anhydrovitamin A. By analogy with the structure proposed for the latter (Meunier, Doulou, and Vinet, *Compt. rend.*, 1943, **216**, 907) the product is tentatively formulated as (IX).

Experimental.

A solution of 1-chloro-3-methylpent-1-en-4-yn-3-ol (20 g.) (Jones and Weedon, *J.*, 1946, 937) in ether (70 c.c.) was added dropwise to a stirred solution of ethylmagnesium bromide (from 7·1 g. of magnesium) in ether (200 c.c.). The mixture was heated under reflux for 5 hours and then cooled. A solution of 2-methyl-4-(2 : 6 : 6-trimethyl*cyclo*hex-1-enyl)but-2-en-1-al (14 g.) (Cheeseman, Heilbron, Jones, Sondheimer, and Weedon, *J.*, 1949, 1516) in ether (50 c.c.) was added dropwise and the mixture was heated under reflux for 5·5 hours and then again cooled. The complex was decomposed by the addition of a saturated aqueous solution of ammonium chloride, and the ethereal layer was then separated, washed with water, dried, and evaporated, the residue being heated at 100°/0·01 mm. whereupon the excess of 1-chloro-3-methylpent-1-en-4-yn-3-ol (10·5 g.) was recovered. A solution of the residual oil (17·4 g.) in light petroleum (b. p. 40—60°; 150 c.c.) was cooled to 0° whereupon a solid (13·7 g.) separated. Recrystallisation from light petroleum (b. p. 60—80°) gave 1-*chloro*-3 : 7-*dimethyl*-9-(2 : 6 : 6-*trimethyl*cyclo*hex*-1-*enyl*)*nona*-1 : 7-*dien*-4-*yne*-3 : 6-*diol* (IV) as needles (9·0 g.), m. p. 121—122° (Found : C, 71·1; H, 8·75. $C_{20}H_{29}O_2Cl$ requires C, 71·3; H, 8·7%). The glycol exhibited no light absorption maximum in the region 2000—4000 Å.

In some experiments it was found advantageous to purify the crude glycol by extracting it with aqueous methanol (80%) from its solution in light petroleum (b. p. 40—60°). Dilution of the pale yellow methanolic extracts with water precipitated the glycol which was then extracted with light petroleum. The extract was dried and cooled whereupon the glycol readily crystallised.

This glycol (0·3 g.) was dissolved in Brady's reagent [from 2 : 4-dinitrophenylhydrazine (0·75 g.), concentrated sulphuric acid (0·8 g.), and methanol (7 c.c.)], and the mixture was kept for 24 hours at 20° during which time a red solid separated. The mixture was cooled to 0°, and the solid filtered off; recrystallisation from light petroleum (b. p. 60—80°) gave a 2 : 4-*dinitrophenylhydrazone* (0·2 g.) as red needles, m. p. 115—117°. This, in view of its mode of formation and light-absorption properties, is formulated as a derivative of the aldehyde (X) (Found : N, 11·6. $C_{27}H_{34}O_6N_4$ requires N, 11·35%). Light absorption in chloroform (main band only) : maximum, 3970 Å; $\varepsilon = 45{,}000$. The 2 : 4-dinitrophenylhydrazone of (VII; R = $CH_2{:}CH{\cdot}C{\equiv}C$) exhibits maximum light absorption in chloroform at 3900 Å ($\varepsilon = 40{,}000$) (Jones and Weedon, *loc. cit.*).

A solution of the acetylenic glycol (1·0 g.) in ethyl acetate (10 c.c.) was shaken in an atmosphere of hydrogen in the presence of a palladium–calcium carbonate catalyst (0·1 g.; 2% Pd) until 70 c.c. of hydrogen had been absorbed. The reaction was then interrupted, the catalyst filtered off, and the solvent evaporated at 20° under reduced pressure, giving the impure glycol (V) as a viscous oil, n_D^{21} 1·5120. Light absorption in alcohol : maximum, 2410 Å; $E_{1\,cm.}^{1\%} = 180$.

The crude product was treated at 20° with Brady's reagent [from 2 : 4-dinitrophenylhydrazine (1·5 g.), concentrated sulphuric acid (1·0 g.), and methanol (10 c.c.)]. The mixture was kept for 2 hours at 0° and the solid (1·15 g.) which separated was removed. This was purified by chomatographic adsorption from benzene solution on a column of partly deactivated alumina and the main, deep red band was eluted with acetone. Evaportion of the solvent under reduced pressure gave a dark red oil (800 mg.), of which an acetone solution was kept at 0°. The crystals (300 mg.) which separated had m. p. 195—197°; light absorption in chloroform (main band only) : maximum, 4350 Å; $E_{1\,cm.}^{1\%} = 850$. Further recrystallisation from the same solvent gave the derivative, m. p. 203° (Found : N, 11·8. Calc. for $C_{34}H_{32}O_4N_4$, N, 12·1%). Light absorption in chloroform (main band only) : 4190 Å; $\varepsilon = 42{,}000$. The m. p. was undepressed on admixture with the derivative prepared from vitamin A by Braude and Forbes (*loc. cit.*), who give m. p. 204° and light absorption in chloroform (main band only) : maximum, 4220 Å; $\varepsilon = 42{,}000$. An authentic specimen of retinene 2 : 4-dinitrophenylhydrazone had m. p. 208° and exhibited maximum light absorption in chloroform at 4450 Å; $\varepsilon = 60{,}000$ (Ball, Goodwin, and Morton, *Biochem. J.*, 1948, **42**, 516, give m. p. 208°, maximum at 4420 Å; $\varepsilon = 54{,}000$).

A solution of the crude glycol (V) (200 mg.), prepared in the manner described above, in toluene (10 c.c.) was heated in an atmosphere of nitrogen on a steam-bath. A solution of iodine (15 mg.) in toluene (3 c.c.) was added in three portions at 5-minute intervals. The solution was then cooled, washed with aqueous sodium thiosulphate solution (2% wt./vol.), and dried and the solvent evaporated under reduced pressure. The residue was dissolved in light petroleum (b. p. 40—60°), and the solution poured on to a column of partially deactivated alumina. The chromatogram was developed with the same solvent and the single broad yellow band was eluted. Evaporation of the solvent gave a yellow oil (120 mg.) which gave a positive Lassaigne test for halogen. Light absorption in *cyclo*hexane : maxima, 3530, 3730, and 3940 Å; $E_{1\,cm.}^{1\%} = 1040$, 1300, and 1100, respectively. Anhydrovitamin A, m. p. 77—78°, exhibits light absorption in *cyclo*hexane : maxima, 3510, 3710, and 3920 Å; $E_{1\,cm.}^{1\%} = 2500$, 3650, and 3180, respectively (Shanz, Cawley, and Embree, *J. Amer. Chem. Soc.*, 1943, **65**, 901).

The authors thank Professors Sir Ian Heilbron and E. R. H. Jones for their interest in this work, Professor R. A. Morton for kindly supplying a sample of retinene, the British Council for a Scholarship (to M. J.), Dr. E. A. Braude for the light-absorption data, and Mr. W. F. Forbes for the mixed melting-point determinations.

Imperial College of Science and Technology,
S. Kensington, London, S.W.7.

[*Received, July 7th*, 1951.]

720. 4 : 5-*Dichloro-o-phenylenediamine.*

By W. Davis and W. C. J. Ross.

4 : 5-Dichloro-*o*-phenylenediamine has been examined as an antimetabolite of 4 : 5-dimethyl-*o*-phenylenediamine which is recognised as a probable precursor of riboflavin and vitamin B_{12} (Woolley, *J. Exp. Med.*, 1951, **93**, 13). Woolley has shown that the dichlorodiamine retards the growth of organisms which do not exhibit a nutritional need for these vitamins : the compound has now been prepared for test as a tumour-growth inhibitor.

Nietzki and Konwaldt (*Ber.*, 1904, **37**, 3892) reduced 1 : 2-dichloro-4 : 5-dinitrobenzene by an unspecified method and showed that the product was an *o*-diamine by preparing a quinoxaline derivative by reaction with benzil—neither the diamine nor the derivative was characterised. Hartley and Cohen (*J.*, 1904, **85**, 865) also obtained a crude form of the diamine. Woolley (*loc. cit.*) prepared the diamine by the reduction of 1 : 2-dichloro-4 : 5-dinitrobenzene or 4 : 5-dichloro-2-nitroaniline, using tin and hydrochloric acid. It has now been found that 4 : 5-dichloro-*o*-phenylenediamine may be more conveniently prepared, in a purer form, by catalytic reduction of these nitro-compounds. The diamine has been characterised by the preparation of a mono- and a di-hydrochloride and a dibenzoate and also by conversion into 6 : 7-dichloro-2 : 3-diphenylquinoxaline and 11 : 12-dichlorophenanthrazine.

Experimental.—4 : 5-*Dichloro-o-phenylenediamine*. A solution of 1 : 2-dichloro-4 : 5-dinitrobenzene (1 g.; Kuhn, Weygand, and Moller, *Ber.*, 1943, **76**, 1044) or 4 : 5-dichloro-2-nitroaniline (1 g.; Nietzki and Konwaldt, *loc. cit.*) in ethanol (70 ml.) containing Raney nickel (1 g.) was shaken in an atmosphere of hydrogen. The theoretical volume of hydrogen was taken up in 15 minutes. The residue obtained after evaporation of the filtered solution under reduced pressure was crystallised from benzene and then from benzene–light petroleum (b. p. 40—60°). The diamine formed colourless, flattened needles, m. p. 163° (Found : C, 41·0; H, 3·0. Calc. for $C_6H_6N_2Cl_2$: C, 40·8; H, 3·4%). Woolley (*loc. cit.*) obtained white or pink crystals which melted at 160° after sintering at 130°.

A stream of dry hydrogen chloride was passed into a solution of the diamine (100 mg.) in dry ether (10 ml.) until precipitation was complete. The product formed colourless plates from alcohol–ether and when sublimed at 100°/0·2 mm. afforded the *monohydrochloride* which decomposed when heated to 200—220° in sealed capillaries (Found : Cl^-, 16·6. $C_6H_6N_2Cl_2$,HCl requires Cl^-, 16·6%).

Hydrogen chloride was passed into a solution of the diamine (100 mg.) in concentrated hydrochloric acid (7 ml.), and the precipitated dihydrochloride was collected, washed with a little concentrated acid, and dried in a vacuum-desiccator. The colourless plates decomposed at 205—220° when heated in sealed capillaries (Found : Cl^-, 28·0. Calc. for $C_6H_6N_2Cl_2$,2HCl : Cl^-, 28·4%). Woolley (*loc. cit.*) obtained white needles which were transformed into plates at 155° and melted with decomposition at 193°.

A suspension of the diamine (60 mg.) in potassium hydroxide solution (20 ml.; 5%) was shaken with benzoyl chloride (0·5 ml.). Slow cooling of an ethanol solution of the product afforded the *dibenzoate* as fine, colourless needles; more rapid cooling produced prisms; both forms had m. p. 257° (Found : C, 62·6; H, 3·8. $C_{20}H_{14}O_2N_2Cl_2$ requires C, 62·4; H, 3·7%).

A solution of the diamine (53 mg.) and benzil (64 mg.) in ethanol (4 ml.) was heated on a steam-bath for 1 hour. Careful addition of water caused the product to crystallise. After recrystallisation from aqueous ethanol the *quinoxaline* formed fine, colourless needles, m. p. 153° (Found : C, 68·6; H, 3·6. $C_{20}H_{12}N_2Cl_2$ requires C, 68·5; H, 3·4%).

Addition of a solution of the diamine (32 mg.), in ethanol (2 ml.), to phenanthraquinone (42 mg.), dissolved in warm acetic acid (3 ml.), caused immediate formation of a flocculent yellow precipitate. 11 : 12-*Dichlorophenanthrazine* forms long yellow needles, m. p. 264°, from acetic acid (Found : C, 69·1; H, 2·6. $C_{20}H_{10}N_2Cl_2$ requires C, 68·8; H, 2·9%).

This investigation was carried out during the tenure by one of the authors (W. C. J. R.) of a British Empire Cancer Campaign Research Fellowship.

The Chester Beatty Research Institute,
Fulham Road, London, S.W.3.

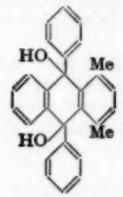
[*Received, July 11th*, 1951.]

721. *Aromatic Hydrocarbons. Part LXII.** 1 : 2-3 : 4-9 : 10-*Tribenzopyrene.*

By E. Clar and J. R. Holker.

1 : 2-3 : 4-9 : 10-Tribenzopyrene (II) was obtained from 9 : 10-dihydro-9 : 10-dihydroxy-1 : 4-dimethyl-9 : 10-diphenylanthracene (I) by the action of copper powder at *ca.* 400°.

(I)



(II)

Experimental.—M. p.s are uncorrected and were taken in evacuated capillaries. Microanalyses were done by Drs. Weiler and Strauss, Oxford.

9 : 10-*Dihydro*-9 : 10-*dihydroxy*-1 : 4-*dimethyl*-9 : 10-*diphenylanthracene.* The Grignard reaction, following Scholl and Meyer (*Annalen*, 1934, **512**, 112), gave a 39% yield of this diol as colourless needles (m. p. 219—220°; lit., m. p. 221—222°). Use of phenyl-lithium gives a higher-melting isomer. To a solution of phenyl-lithium from lithium chips (2·7 g.) in ether (100 c.c.) and bromobenzene (32 g.) in ether (100 c.c.), 1 : 4-dimethylanthraquinone (20 g.) was added in portions, and the solution was refluxed for 30 minutes. After decomposition of the mixture, the ether was distilled off and the residue extracted with alkaline dithionite (hydrosulphite). The yield of product was 28 g. and the m. p. 215—245° (decomp.). Extraction with boiling alcohol (150 c.c.) left a residue (17·5 g.) of m. p. 254—258°, raised by further extraction with benzene to 259—262°. Crystallisation from xylene lowered the m. p. to 213—215°. The diol, m. p. 259—262°, and the diol, m. p. 221°, both gave only 1 : 4-dimethyl-9 : 10-diphenylanthracene (Dufraisse and Horclois, *Bull. Soc. chim.*, 1936, **3**, 1900) on reduction with potassium iodide and sodium hypophosphite in acetic acid.

1 : 2-3 : 4-9 : 10-*Tribenzopyrene.*—The diol, m. p. 221° (2 g.), and copper powder (0·2 g.) were heated at 400° in carbon dioxide for 3 hours. Extraction with benzene, concentration, and dilution with light petroleum yielded a gum which was removed. Concentration of the mother-liquor to a very small volume and cooling gave an orange-yellow powder, which on recrystallisation from very little benzene yielded 25 mg. of 1 : 2-3 : 4-9 : 10-*tribenzopyrene*, m. p. 236—238°. Similar treatment of the diol, m. p. 254—258 (10 g.), followed by distillation (320°/2 mm.), gave small orange plates, m. p. 238° (175 mg.), from benzene (Found: C, 94·7; H, 4·6. $C_{26}H_{16}$ requires C, 95·4; H, 4·6%). The hydrocarbon showed a green fluorescence in organic solvents and gave a green solution in sulphuric acid, becoming brown on storage.

University of Glasgow. [*Received, July 13th*, 1951.]

* Part LXI, *J.*, 3215.

OBITUARY NOTICE.

JOSEPH HENRY LANE.

1883—1951.

JOSEPH HENRY LANE was born in London in 1883. He received his early education at Raine's School, Stepney, and his scientific training at Finsbury Technical College under Professor Raphael Meldola and Frederick William Streatfeild. After graduation he remained at Finsbury for a time as research assistant to Professor Meldola and in 1903 and 1904 collaborated in two papers, on the isomeric aminoamidines of the naphthalene series, that were published in the *Journal*.

In 1904 he accepted an appointment in the laboratory of the Beet Sugar Association, subsequently to become the Sugar Association of London, and entered upon what was to become his main interest in life. In the laboratory of the Sugar Association he met Mr. Lewis Eynon, with whom, on the closing of the Sugar Association's laboratory in 1910, he entered into partnership as a consulting chemist, specialising in the analysis of sugars and in the chemistry of fermentation.

He was admitted to Fellowship of the Society in 1941, and was a Fellow of the Royal Institute of Chemistry.

Between the years 1909 and 1931 his published work included eight papers and two monographs.

Of his published work the most important was the paper on methylene blue as an internal indicator in the volumetric determination of the reducing sugars by Fehling's solution. His collaborator in this work, Mr. Lewis Eynon, has placed it upon record in *The Analyst* that Lane played the principal part in this discovery, but many laborious months were spent by the partners in experimental verification of its accuracy and precision and in the preparation of the series of factorial tables for the various reducing sugars, which have remained in use to the present time.

According to Lane's own account, he and his partner had already spent much time in trying to improve upon the unsatisfactory external indicators, such as potassium ferrocyanide, ferrous thiocyanate, and a mixture of potassium iodide and starch, then in use; and as he stood one day in his laboratory, surrounded by numerous samples on which determinations of reducing sugars were required to greater accuracy than could be attained otherwise than by the laborious and lengthy gravimetric method, he wondered if he could find a dye that would act in a sugar titration like some of those that were just then coming into use as oxidation–reduction indicators. So he examined his collection of reagents and seeing a bottle of methylene-blue, he tried it—with the result that we all know to-day.

The methylene-blue method immediately gained world-wide recognition. C. L. Hinton wrote of it in 1930 (" Recent Advances in Analytical Chemistry," Ed. C. Ainsworth Mitchell, J. & A. Churchill, London, 1930) : " The introduction by Lane and Eynon of methylene-blue as an internal indicator was an advance of the first order. So great has been the gain, in fact, that R. F. Jackson recently stated (*J. Assoc. Off. Agric. Chem.*, 1929, **12**, 166) that ' the method is, on account of its convenience, accuracy, and rapidity, largely displacing the gravimetric methods for reducing sugar '." Hinton's statement is as true to-day as when it was first made, twenty years ago. There are not many analytical methods that have stood the test of time so well.

Lane was for many years an abstractor for *J. Soc. Chem. Ind.* and *J. Inst. Brewing*. This brought him a wide experience of the literature of analytical chemistry, which, combined with his ability to write clear, concise English, he turned to good account when he was appointed Assistant Editor to *The Analyst* (in succession to T. H. Pope) in 1936 and Editor in 1945, on the retirement of Dr. Charles Ainsworth Mitchell. He succeeded Mitchell as Secretary of the Society of Public Analysts and Other Analytical Chemists in 1937.

Lane was of a kindly, cheerful, and generous disposition, ever ready to place his knowledge and experience, freely and in full, at the disposal of others. Time and trouble counted for nothing where he could be of help.

" Good temper triumphed in his face,
And in his heart he found a place
For all the erring human race . . ."

During his last year of life he bore increasing bodily weakness with great fortitude and remained cheerful to the end, which came to him at Taplow on the 9th March, 1951.

F. L. OKELL.

THE CHEMICAL SOCIETY

SCIENTIFIC MEETINGS DURING DECEMBER, 1951

LONDON.

Thursday, December 13th, 1951, at 7.30 p.m.

Tilden Lecture, **Some Recent Developments in the Chemistry of Free Radical Reactions in Solution,** by Professor D. H. Hey, D.Sc., F.R.I.C.

ABERDEEN.

Friday, December 14th, 1951, at 7.30 p.m.

Lecture, **The Trout's Habitat,** by Mr. A. Dargie, B.Sc., A.R.I.C.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, to be held in the Chemistry Department, Marischal College, Aberdeen.

BIRMINGHAM.

Friday, December 7th, 1951, at 4.30 p.m.

Lecture, **Cortisone,** by Professor C. W. Shoppee, D.Sc., F.R.I.C.

Joint meeting with the University Chemical Society to be held in the Chemistry Lecture Theatre, The University, Edgbaston, Birmingham.

BRISTOL.

Thursday, December 6th, 1951, at 7 p.m.

Lecture, **Chemical Engineering Applied to the Fertilizer Industry,** by Mr. R. P. Ross, B.Sc.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, to be held in the Chemistry Department, The University, Bristol.

EDINBURGH.

Thursday, December 13th, 1951, at 7.30 p.m.

Lecture, **The Assimilation of Amino Acids by Bacteria,** by Dr. E. F. Gale.

Joint meeting with the local sections of the Royal Institute of Chemistry and the Society of Chemical Industry, to be held at the North British Station Hotel.

IRISH REPUBLIC.

Wednesday, December 12th, 1951, at 7.45 p.m.

Lecture, **Novel Cytotoxic Agents,** by Dr. F. L. Rose, O.B.E.

To be given in the Chemistry Department, Trinity College, Dublin.

LIVERPOOL.

Thursday, December 6th, 1951, at 5 p.m.

Lecture, **New Developments in Methods for Following Fast Chemical Reactions,** by Professor H. W. Melville, D.Sc., F.R.S.

To be given in The Chemistry Lecture Theatre, University of Liverpool.

MANCHESTER.

Friday, December 7th, 1951, at 6.30 p.m.

Lecture, **Scientific Problems in D.S.I.R.,** by Sir Ben Lockspeiser, F.R.S.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, to be held at the Engineers' Club.

NORTH WALES.

Thursday, December 6th, 1951, at 5.45 p.m.

Lecture, **Chemistry and Atomic Power,** by Dr. R. Spence, F.R.I.C.

Joint meeting with the Royal Institute of Chemistry and University College of North Wales Chemical Society, to be held in the Department of Chemistry, University College of North Wales, Bangor.

NORTHERN IRELAND.

Friday, December 14th, 1951, at 7.15 p.m.

Lecture, **The Industrial Utilisation of Agricultural By-products,** by Dr. F. N. Woodward, B.Sc., F.R.I.C.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry, to be held in the Department of Agricultural Chemistry, Queen's University, Belfast.

NOTTINGHAM.

Thursday, December 6th, 1951, at 4.45 p.m.

Lecture, **New Notation for Organic Compounds,** by Dr. G. M. Dyson, F.R.I.C.

Joint meeting with the University Chemical Society to be held in the University, Nottingham.

SOUTHAMPTON.

Friday, December 7th, 1951, at 5.0 p.m.

Lecture, **Some Recent Developments in the Chemistry of the Heaviest Elements,** by Dr. J. S. Anderson, M.Sc., A.R.C.S.

Joint Meeting with Southampton University College Chemical Society to be held in the Physics Department, University College, Southampton.

PROCEEDINGS

OF THE

CHEMICAL SOCIETY

Minutes of a

SCIENTIFIC MEETING

held at Burlington House on October 18th, 1951, at 7.30 p.m.

The President, SIR ERIC RIDEAL, M.B.E., M.A., D.Sc., F.R.S., was in the Chair, and welcomed Professor F. G. Soper, C.B.E., the Society's Representative in New Zealand, who was present.

MINUTES.

The Minutes of the Scientific Meeting held in the Lecture Theatre of The Royal Institution on June 7th, 1951, circulated in the Proceedings for July, 1951, were taken as read, and were confirmed and signed.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: K. S. Sutherland, Harold H. Burns, R. A. Abramovitch, G. G. Jackson, Michael G. Ball, G. Jacobowitz, H. Irwin, George W. Ross, A. Gordon Elliott, D. R. Hogg, P. F. Clark, K. R. H. Wooldridge, J. Patricia Brown, Freda Bowyer, Brian Stannard, Michael J. Kenney, Alan P. MacKenzie, E. W. Hasler, E. G. Ansell, R. A. Heacock, H. N. Mortlock, L. Horsman, A. L. Green, C. S. Barnes, H. Rosenberg, A. Sidle, J. M. Wentworth, A. L. Glenn.

TILDEN LECTURE.

After a brief introduction, the President called upon Professor C. A. Coulson, F.R.S., to deliver the Tilden Lecture entitled "The Contributions of Wave Mechanics to Chemistry." At the conclusion of the lecture, a vote of thanks, proposed by Professor T. S. Wheeler, was carried with acclamation.

OFFICIAL ANNOUNCEMENTS

DEATHS.

The Council regrets to announce the deaths of the following Fellows:

	Elected.	Died.
James Baddiley (Sale)	July 7th, 1947.	Sept. 25th, 1951.
Charles Wesley Bayley (S.E.1)	May 7th, 1914.	Aug. 22nd, 1951
Ray Arthur Patelski (New York)	Nov. 11th, 1948	Sept. 7th, 1951.
Edmund George Vincent Percival (C. 1949—) (Edinburgh).....	Dec. 7th, 1933.	Sept. 27th, 1951.

*

ELECTION OF NEW FELLOWS.

The following 53 candidates were elected Fellows of the Society on October 18th, 1951 :

Ibrahim Ali Ammar.
Gordon Bruce Barlin.
James Richard Keith-Bartels.
Henry Hermann Bauer.
Lionel John Bellamy.
Sachindra Kumar Bhattacharyya.
Edward John Blackman.
William Harold Bowe.
Thomas Broadhurst.
Kenneth Bateson Bull.
Barbara Sybil Burwell.
Arthur Busby.
Eskild Sorensen-Byrge.
Yu-wei Chang.
Subodh Chandra Chatterjee.
Thomas Peter Cooper.
Robert Charles Doban.
Peter Godwin Embrey.
Thomas Richard Farnworth.
Wilhelm Flöttmann.
David Gall.
Frederick James Gallion.
Fred J. Gerecht.
Harry Harker.
Marion Frederick Hawthorne.
Harold Warren Heine.
Brenda Frances Hill.
Charles William Jefford.
Leonard Korn.
Rex Everett Lidov.
Geoffrey Lord.
Maurice Pierre Metayer.
John Edward Osborne.
Ogden Ross Pierce.
Frank James Pinchin.
Madan Krishnarao Pradhan.
Anthony Maitland Roe.
Mario Giuseppe Samassa.
Frederic Duncan Shaw.
Lionel Louis Shreir.
Richard Lucien Spiller.
David Frederick Stewardson.
Robert James Stewart.
Adam Zygmunt Szumer.
Jacob Szmuszkovicz.
William James Orville Thomas.
Mrs. Jean Margaret Eveline Travers.
Johannes Van Ormondt.
Zdenek Jaromir Vejdelek.
Michael Owen Welch.
Keith Desmond Eric Whiting.
John Gerald Wilson.
Mrs. June Zealley.

VACANCY ON COUNCIL—CONSTITUENCY V.

Dr. N. Campbell has been co-opted under Bye-Law 42 as a Member of Council to fill the vacancy caused by the death of Dr. E. G. V. Percival, and to serve until the next Annual General Meeting.

THE LIBRARY.

The Library will be closed for the Christmas holidays from Saturday, December 22nd, at 1 p.m., until Friday, December 28th, at 10 a.m.

PUBLICATIONS OF THE AMERICAN CHEMICAL SOCIETY.

The following are the rates for 1952 at which Fellows may purchase publications of the American Chemical Society :

	Price to Public.	Price to Fellows of The Chemical Society.	Postage.
	$.	$.	$.
Journal of The American Chemical Society	14.00	12.60	3.00
Industrial Engineering Chemistry	5.00	4.50	2.70
Analytical Chemistry	4.00	3.60	1.20
Industrial and Engineering Chemistry and Analytical Chemistry (combination)	8.00	7.20	3.90
Chemical and Engineering News	6.00	5.40	2.25
Chemical Abstracts, complete Abstract issues and annual author, subject, patent and formula indexes and rights to A.C.S. Photocopying Service	60.00	54.00	2.70
Chemical Abstracts, Abstracts issues only	24.00 *	21.60 *	2.70
Journal of Physical Chemistry	10.00	9.00	1.20

* Sold only to subscribers to the complete set listed above.

Applications should be made direct to the American Chemical Society, 1155, Sixteenth Street, N.W., Washington, D.C., U.S.A., and it should be noted that permission to remit money abroad must be obtained through a bank.

ROYAL PHOTOGRAPHIC SOCIETY—SCIENTIFIC AND TECHNICAL GROUP.

Fellows of the Chemical Society may attend meetings arranged by the Scientific and Technical Group of the Royal Photographic Society, and receive notices of all meetings arranged by the Group on payment of an annual subscription of five shillings. Fellows wishing to learn further details should apply to Dr. R. B. Collins, Convenor, Programme Committee, Scientific and Technical Group, The Royal Photographic Society (Ilford, Ltd., Ilford, Essex).

LIST OF APPLICATIONS FOR FELLOWSHIP

(Fellows wishing to lodge objection to the election of these candidates should communicate with the Honorary Secretaries within ten days of the date of publication of the " Journal *" for November,* 1951. *Such objections will be treated as confidential. The forms of application are available in the Library.)*

***Badsey, Geoffrey Buxton Weeks,** B.Sc. (Lond.). British. 20, Islington Street, Swindon, Wilts. Laboratory Assistant, I.C.I. (Plastics Division), Welwyn Garden City. *Signed by:* J. W. C. Crawford, A. W. Jukes, M. Clasper.

***Barlow, Geoffrey Brian,** M.Sc. (Birm.). British. Chemistry Department, The University, Birmingham 15. Research Student. *Signed by:* L. L. Bircumshaw, S. R. Carter, L. F. J. Parker.

Barlow, David Osher, B.Sc. (Washington). American. Bagley Hall, University of Washington, Seattle, Washington, U.S.A. Graduate Student. *Signed by:* Kenneth B. Wiberg, H. J. Dauben, Arthur R. Anderson.

Bayly, Russell James, B.Sc. (Birm.). British. 51, Heron Court Road, Bournemouth, Hants. Assistant Lecturer, Birmingham University. *Signed by:* E. J. Bourne, F. W. Pinkard, K. Butler.

Bohm, Emanuel, R.N.Dr., Ph.D. (Prague). Slovak. 79, Messina Avenue, London, N.W.6. Food Chemist, Research Laboratories, 27, St. Paul's Way, London, E.3. *Signed by:* M. C. Schaul, B. Deutsch, V. Jones.

Broadbank, Robert William Clayson, B.Sc. and Ph.D. (Lond.), A.R.I.C. British. 41, High Street, Hillmorton, Rugby, Warwickshire. Senior Lecturer, School of Chemistry, College of Technology, Leicester. *Signed by:* E. D. Hughes, D. P. Craig, F. R. Mumford.

***Caldwell, Eric Victor,** B.Sc. (Lond.). British. 18, Gardner Road, Plaistow, E.13. Research Student, Birkbeck College. *Signed by:* R. C. Mehrotra, D. C. Bradley, W. Wardlaw.

***Claussen, Brian Harry,** B.Sc. (Lond.). British. 22, Collinwood Gardens, Ilford, Essex. Research Student, Queen Mary College, E.1. *Signed by:* C. M. French, D. F. Muggleton, R. F. Garwood.

***Clingman, Abraham Lionel,** B.Sc. (Rand). South African. National Chemical Research Laboratories, P.O. Box 395, Pretoria, South Africa. Chemist. *Signed by:* D. A. Sutton, W. S. Rapson, D. H. S. Horn.

Czarnikau, Johanna. British. 24, Devonshire Terrace, London, W.2. Chemist. British Celanese, Ltd. *Signed by:* B. A. Hext, H. L. Peerman, J. C. Everett.

***Davis, Richard John,** B.A. (Oxon.). British. 10, Milverton Road, Brondesbury Park, N.W.6. Research Chemist, North Thames Gas Board. *Signed by:* W. A. Waters, D. G. Thomas, B. B. Goalby.

Dunderdale, John, B.Sc. (Lond.). British. 24, Parliament Road, Middlesborough, Yorks. Student. *Signed by:* E. D. Hughes, C. K. Ingold, G. J. Bullen.

***Dunn, John Robert,** B.Sc. (Lond.). British. Balliol College, Oxford. Research Student. *Signed by:* W. A. Waters, R. F. Moore, C. Wickham-Jones.

***Eaton, David Crawford,** B.Sc. (Manc.). British. 48, London End, Beaconsfield, Bucks. Research Chemist, Manchester University. *Signed by:* H. B. Henbest, J. B. Armitage, P. Bladon.

***Elliott, Joseph Holroyd.** British. 15, Wesley Street, Cleckheaton, Yorks. Student at Leeds University. *Signed by:* R. B. Hardwick, H. Bing, F. Challenger.

Ferguson, Ian Forster. British. 33, Newlands Avenue, Shirley, Southampton. Student at University College, Southampton. *Signed by:* K. R. Webb, F. D. Hills, R. E. Parker.

Fitt, John Stanley, B.Sc. (Lond.), A.R.C.S. British. 11, Bracknell Gardens, London, N.W.3. Research Student, Imperial College. *Signed by:* R. P. Linstead, J. A. Elvidge, Margaret Whalley.

***Fuller, Keith William.** British. 35, Parkside, Cambridge. Student at Cambridge University. *Signed by:* P. Sykes, D. Stockdale, A. M. Parsons.

Gaze, Richard, B.Sc. (Lond.). British. 14, Rectory Gardens, Cranham, Essex. Chief Chemist, The Cape Asbestos Co., Ltd., Barking. *Signed by:* D. C. Hancock, R. C. Mehrotra, D. C. Bradley.

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PAPERS RECEIVED

(List of papers received between September 17th and October 16th, 1951.)

"Organic fluorides. Part XI. Fluorination of heterocyclic compounds with cobalt trifluoride." By R. MONTGOMERY and F. SMITH.

"Lanthanon complexes with ethylenediamine-*NNN'N'*-tetra-acetic acid. Part III." By R. C. VICKERY.

"Some *N*-substituted derivatives of poly-(α-aminoacrylic acid)." By M. FRANKEL and M. E. REICHMANN.

"The reaction of sodiomalonic ester with a halogeno-carboxylic acid." By M. D. POTTER and E. P. TAYLOR.

"Synthetic analgesics and related compounds. Part III. The aminoalkylation of phenyl-substituted acetones." By W. WILSON.

"5-Hydroxy-1 : 2-benzanthracene and 1'-hydroxy-1 : 2-5 : 6-dibenzanthracene." By J. W. COOK and (MISS) R. SCHOENTAL.

"New syntheses of heterocyclic compounds. Part XIII. 2-Amino-3 : 5-dimethyl-1 : 4-diazaphenanthrenes (continued)." By A. COURTS and V. PETROW.

"Identification of *iso*dinaphthylene oxide as dinaphtho(2' : 3'-2 : 3)(1'' : 2''-4 : 5)furan; some functional derivatives of the latter." By NG. PH. BUU-HOÏ.

"1 : 2 : 5 : 6-Tetrachloronaphthalene." By H. A. PIGGOTT and F. H. SLINGER.

"Enzymic synthesis and degradation of starch. Part XV. β-Amylase and the constitution of amylose." By S. J. PIRT, W. J. WHELAN, and S. PEAT.

"The enzymic synthesis and degradation of starch. Part XVI. The purification and properties of the β-amylase of soya bean." By S. J. PIRT, W. J. WHELAN, and S. PEAT.

"The enzymic synthesis and degradation of starch. Part XVII. Z-Enzyme." By GWEN J. THOMAS, W. J. WHELAN, and S. PEAT.

"The catalytic deuteration of organic compounds. Part I. Deuteration and disproportionation." By J. BELL and S. J. THOMSON.

"The catalytic deuteration of organic compounds. Part II. The deuteration of cholesterol and ergosterol." By J. BELL and S. J. THOMSON.

"The chemistry of ethylene oxide. Part IV. The kinetics of the reaction of ethylene oxide in pyridine solutions of hydrogen halides." By A. M. EASTHAM.

"Anionic polymerisation. Part I. The polymerisation of styrene in liquid ammonia solution catalysed by potassamide." By W. C. E. HIGGINSON and N. S. WOODING.

"Anionic polymerisation. Part II. The acid–base character of anionic polymerisation." By N. S. WOODING and W. C. E. HIGGINSON.

"Anionic polymerisation. Part III. Some observations on the polymerisation of styrene in liquid ammonia catalysed by potassium." By N. S. WOODING and W. C. E. HIGGINSON.

"Heterocyclic fluorides from diazonium silicofluorides." By R. D. BEATY and W. K. R. MUSGRAVE.

"The compound of boron trichloride with dioxan." By A. K. HOLLIDAY and JOAN SOWLER.

"Oxindoles formerly regarded as ψ-indoxyls." By R. F. MOORE and S. G. P. PLANT.

"Diamidides. Part II. 2 : 4-Diaryltriazapentadienes." By D. A. PEAK.

"The elimination of non-angular alkyl groups in aromatisation reactions. Part I." By WESLEY COCKER, BRIAN E. CROSS, and (MISS) JOAN MCCORMICK.

"Solutions of alcohols in non-polar solvents. Part II. Volume relation in dilute solutions of primary alcohols in benzene, heptane, and *cyclo*hexane." By L. A. K. STAVELEY and (MISS) BETTY SPICE.

"Research in the menthone series. Part XVII. Configurations of menthols and menthylamines." By NEAL L. MCNIVEN and JOHN READ.

"Researches in the carvone series. Part V. Configurations of carvomenthones and carvomenthylamines and their steric relation to menthones." By NEAL L. MCNIVEN and JOHN READ.

"The synthesis of *N'*-formyl-DL-kynurenine, N^{α}-acetyl-DL-kynurenine, and related compounds, and observations on the synthesis of kynurenine." By C. E. DALGLIESH.

"The constitution of yohimbine and related alkaloids. Part VI. The synthesis of 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-octahydro-2-ketoindolo(2 : 3-*a*)quinolizine and 1 : 2 : 3 : 4-tetrahydroindolo(2 : 3-*a*)quinolizine." By L. H. GROVES and G. A. SWAN.

"Synthesis of carbohydrates by use of acetylenic precursors. Part II. Addition reactions of *cis*- and *trans*-but-2-ene-1 : 4-diol diacetates. Synthesis of DL-erythrulose." By R. A. RAPHAEL.

"A synthesis of histamine from but-2-yne-1 : 4-diol." By M. M. FRASER and R. A. RAPHAEL.

"New syntheses of heterocyclic compounds. Part XIV. Some new derivatives of 1 : 3-dimethyl-2-azafluorene." By B. N. FEITELSON and V. PETROW.

"A synthesis of vitamin A from *cyclo*hexanone." By J. ATTENBURROW, A. F. B. CAMERON, J. H. CHAPMAN, R. M. EVANS, B. A. HEMS, A. B. A. JANSEN, and T. WALKER.

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" Steroids and related compounds. Part XIII. The preparation of 21-hydroxypregna-4 : 17-dien-3-one." By D. K. PATEL, V. PETROW, R. ROYER, and (MRS.) I. A. STUART-WEBB.

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